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A PRELIMINARY INVESTIGATION OF THE THERAPEUTIC VALUE OF LANATOSIDE C (DIGILANID C)

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TWO hundred fifty-six patients with heart disease who have been admitted to the Minneapolis General Hospital since October, 1937, and treated with the recently isolated, crystalline, stable glycoside, lanatoside C (Digilanid C)* have exhibited rapid and efficient clinical responses. In cases of auricular fibrillation, a dramatic slowing of the heart rate was frequently observed a few minutes after intravenous administration of the drug; cardiac failure in the presence of normal sinus rhythm disappeared more rapidly than in a control series in which no digitalis was given; some hyperthyroid patients with auricular fibrillation responded promptly with a slowing of the heart rate; and, in a relatively high percentage of cases, cardiac arrhythmias were quickly replaced by normal sinus rhythm. Toxic reactions were rare, and a few patients who had been unable to tolerate digitalis took lanatoside C with a good therapeutic result.

Our results indicate that this drug should now have a wide clinical trial, so that we may be fully informed as to its advantages over the usually employed purpurea preparations.

Digitalis lanata contains a glycoside, lanatoside C, which has no chemical relationship with the glycosides of digitalis purpurea. It occurs exclusively in the digitalis lanata species and is chemically marked by the structure of its aglucone digoxigenin, which, as has been shown by Smith,[1] differs considerably from the genins of the other glycosides which are derived from digitalis lanata and purpurea. However, the exact relationship between these two digitalis plants was not understood until the publication of the exhaustive studies of Stoll,[2] which resulted

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*The Committee on Nomenclature of the Council on Pharmacy and Chemistry of the A. M. A. recently accepted the terms lanatoside A, lanatoside B, and lanatoside C as scientific (nonproprietary) names for the three cardioactive glycosides isolated from the leaves of digitalis lanata. In the early clinical literature lanatoside C is referred to as Digilanid C.

in the isolation of all of the cardioactive glycosides of digitalis lanata and purpurea, together with the products of their enzymatic hydrolysis.

The digitalis glycosides consist of an aglucone or genin nucleus, linked by a side chain to a variable number of sugars. The aglucones have been designated as the carriers of the cardioactive properties, but, when deprived of their sugars, they are practically insoluble in water, scarcely absorbable, and devoid of fixation power. It may thus be assumed that the therapeutic properties of a cardioactive glycoside are to a certain extent determined by the sugars which are linked to the aglucone. The lanatosides A, B, and C comply with this idea because they are crystalline, stable, adequately soluble glycosides of high carbohydrate content.

Because lanatoside C is a crystalline substance, biologic assay is not necessary, and its dosage may be determined gravimetrically, rather than by the "cat unit" method, once the therapeutic efficacy is established. Since it is a chemically pure substance which contains no enzymes, lanatoside C is not subject to changes in potency over a period of years, as are galenic preparations.

In 1938, Moe and Visscher[3] completed a pharmacologic study of lanatoside C. This work showed that lanatoside C is a drug which greatly increases the mechanical efficiency of the failing heart, and, at the same time, has the highest ratio of therapeutic to toxic effect of any of the cardioactive glycosides which they investigated. Moreover, Essex, Herrick, and Visscher,[4] in 1938, demonstrated that lanatoside C, in therapeutic doses, did not reduce the flow of blood through the coronary arteries of the dog. From a study of Visscher and Moe's and Visscher, Herrick, and Essex's work, we came to the conclusion that lanatoside C would probably be a useful drug in the treatment of heart failure and determined to make an extensive study of its therapeutic effect on patients.

Bauer,[5] Hu, Lien, and Li,[6] and Büchner[7] have shown that digitoxin, the most toxic glycoside of digitalis purpurea, when administered in large doses, will cause degenerative changes in the heart muscle of dogs within thirty days. The doses used were far in excess of those given clinically, but their results suggest that degenerative changes may be produced by digitalis glycosides. Hence, we thought it advisable to conduct similar experiments with lanatoside C.

We gave large quantities of lanatoside C (as much as five times the therapeutic dose) daily, to dogs, over periods of one to three months. One 32-pound dog received 1.25 mg. of the drug by mouth daily for three months, which is equivalent to 6.75 mg., or 25 cat units, daily for a 160-pound man. An exceedingly careful histologic examination of this dog's myocardium by Dr. Clawson, of the Department of Pathology, together

with Dr. LaDue, revealed no abnormalities. Another dog, which was given 1.5 c.c. (0.3 mg.) intravenously every day for thirty days, was also found to have a histologically normal heart muscle. This is equivalent to the amount given intravenously for complete digitalization in man and would never be given daily.

These experiments are being repeated with larger doses, but we have sufficient data at the present time to conclude that it is highly probable that lanatoside C can be given in therapeutic doses to man over long periods of time without danger of producing morphologic changes in the myocardium.

Lanatoside C was supplied by the Sandoz Chemical Works, Inc., in tablet form, and in ampules for intravenous use. Each tablet contained 0.25 mg. of lanatoside C,* and each cubic centimeter of solution, 0.20 mg. of the drug. According to Rothlin[8] and Visscher,[9] 0.28 mg. of the drug is equivalent to an international Magnus-DeLind cat unit.

METHOD OF INVESTIGATION

Clinicians agree that digitalis is efficient in the treatment of heart failure accompanied by auricular fibrillation. For the physician who practices without the aid of venous pressure and vital capacity measurements, the slowing of the heart rate following the administration of a digitalis preparation in cases of auricular fibrillation is considered one of the most reliable indications of therapeutic response.

For this reason, we began our study by selecting only patients with auricular fibrillation and heart rates above 120 who had not taken any digitalis preparation for at least three weeks. The amount of lanatoside C needed to stabilize the heart rates of these patients below 85 determined the so-called "digitalizing dose" which we now use in all cases of heart failure and in certain arrhythmias.

Reports on lanatoside C,[10] to date, say nothing of a "digitalizing dose," but advise giving two to eight tablets a day, or, for patients with severe heart failure, 2 to 4 c.c. intravenously. Although no average rate of action has been given, the case reports of previous investigators show a much slower response (from two to ten days for a decline in pulse rate, etc.) than we have obtained.

Individual records were kept on all of our patients. On admission, the heart rate was counted at the apex for one full minute, and again every two hours thereafter until it fell to 85, or below. The venous pressure and vital capacity were measured at the same time, and at least once daily throughout the period of cardiac failure. A daily chart recorded these measurements, the fluid intake and output, the degree of dyspnea, orthopnea, and cyanosis, and the variations in peripheral and pulmonary edema, as well as hepatic enlargement, together with clinical notes concerning the subjective state of the patient. No diuretics or other drugs were given, except sedatives, usually morphine or phenobarbital, as needed to secure rest or relief from cough or pain. Only when collections of fluid in the serous cavities threatened the life of the patient was salyrgan given or a paracentesis done. The fluid intake was limited to 800 c.c. a day. Urinalyses, and blood and serologic studies were ordered routinely; teleoroentgenograms were taken on admission and discharge, and electrocardiograms were made frequently. Thus, a quantitative, as well as a qualitative, measure of the day-by-day cardiac status of each patient was secured.

*Lanatoside C (Cedilanid, Sandoz Chemical Works, Inc.) is now put up in tablets containing 0.5 mg.

USE IN THE PRESENCE OF AURICULAR FIBRILLATION

To date, 102 patients with auricular fibrillation* have received lanatoside C. It must be emphasized that there was no selection of cases; patients were treated regardless of age, sex, type of heart disease, or severity of heart failure, except that patients with coronary thrombosis and patients who had been taking therapeutic doses of digitalis were excluded.

Lanatoside C was first given in doses of one tablet (0.25 mg.) four times a day until the pulse rate fell to 85, or below. These early patients required eight to forty-eight tablets to slow the pulse rate within two to twelve days. Larger doses were therefore given, and the digitalizing amount best suited to the majority of patients was found to be an initial dose of fifteen tablets, followed within twelve to twenty-four hours by ten additional tablets, given in single or divided doses. The exact relation of dosage to weight has not yet been ascertained, but women usually require slightly less lanatoside C for maintenance than men.

AURICULAR FIBRILLATION.
WITH INTRAVENOUS LANATOSIDE C

TIME.	PULSES.						
	>150	150-140	140-130	130-120	120-100	100-90	<90
0-30 MIN.	•	•	••	••	••	•	
30-60 MIN.	••	••	••• •		•		
1-2 HRS.	•••• •	•••••• •	•••• ••	••••• •	•		•
2-3 "	•		•				
3-5 "		•	•	•			
5-12 "	•	• •					
12-24 "			•	•	•		
24-48 "	•			•	•		
48-72 "							
3-7 DAYS.			•	•	•	•	
7+ DAYS.							
TOTALS.	11	13	16	12	7	2	1

Fig. 1.—This table shows the time required, after the intravenous administration of lanatoside C, for the heart rate to fall to 85, or lower. The circles represent patients who died at varying intervals after the administration of the drug and the decline in heart rate. Cases in which the heart rate was originally less than 100 have no significance with respect to the time at which the fall in heart rate to 85, or below, occurred.

After several months' experience with the oral preparation, intravenous administration was begun. Ampules containing 0.2 mg. of lanatoside C per cubic centimeter were obtained, and an attempt was

*Cases of paroxysmal auricular fibrillation were not included, nor were cases of auricular fibrillation associated with hyperthyroidism.

made to give the "digitalizing dose" in one injection. Trials of 2, 4, 6, and 8 c.c. injections were made before a dose of 8 c.c. was chosen as the optimal digitalizing dose for adults.

Fig. 1 shows the rapidity with which the heart rates of fifty-two patients fell to 85, or lower, when 8 c.c. of lanatoside C were given intravenously. Thirty-eight patients responded with a slowing of the pulse rate to 85 (or lower) in less than two hours. Two required twelve to twenty-four hours; two, twenty-four to forty-eight hours; and two, forty-eight to seventy-two hours. These intervals were longer than may actually be expected, for twenty patients who were classified as having responded within "one to two hours" had their pulse rates checked only every two hours, and some of them undoubtedly responded more promptly. A detailed study of fifteen consecutive patients whose heart rates were counted every five minutes following the injection of 8 c.c. of lanatoside C gave a more accurate index of the rapidity of the drug's action. All had heart rates of more than 120, after twenty-four to forty-eight hours of rest in bed, but slowing of the pulse rate to 85, or less, occurred within two to ninety minutes, with a mean time of thirty minutes, after the administration of the drug.

AURICULAR FIBRILLATION.
WITH ORAL LANATOSIDE C

TIME.	PULSES.				
	>140	140-120	120-100	100-90	<90
0-30 MIN.					●●●●● ●●●●● ● ●
30-60 MIN.				●	
1-2 HRS.			●		
2-3 "					
3-5 "					
5-12 "			●		
12-24 "	●●	●●●	● ●●		
24-48 "	●	●●● ●●	●●●	●●	
48-72 "		●● ●	●		
3-7 DAYS.	●		●		
7+ DAYS.					
TOTALS.	4	11	10	3	12

Fig. 2.—This shows the time required, after the oral administration of lanatoside C, for the heart rate to fall to 85 per minute, or lower. The circles represent patients who died at varying intervals after the decline in pulse rate. The first horizontal column indicates what the heart rates were at the time of administration of the drug. Patients whose heart rates were originally less than 100 are included, but the data in these cases have no significance with respect to the time at which the fall in heart rate to 85, or lower, occurred.

The response of patients with auricular fibrillation to the oral administration of lanatoside C is also more rapid than the average time indicated in Fig. 2, since the results in twenty-five early cases, in which

insufficient digitalizing doses were given, are included. Two of these early cases appear in the three- to seven-day group, three in the forty-eight- to seventy-two-hour group, six in the twenty-four- to forty-eight-hour group, and one falls in the twelve- to twenty-four-hour group. All patients who received twenty-five tablets of lanatoside C within twenty-four hours responded with a slowing of the pulse rate within forty-eight hours after the administration of the first dose. In more than half of these cases the slowing occurred within twenty-four hours.

When given intravenously, lanatoside C's rapidity of action may be compared to that of strophanthin, and, when administered by mouth, it acts as fast as any oral preparation of digitalis purpurea.

We have given lanatoside C to twelve patients with auricular fibrillation whose heart rates were less than 90. In two cases the venous pressure was above 15 cm. of saline and fell to normal three days after 8 c.c. of lanatoside C were given intravenously. Six patients received twenty-five tablets (6.25 mg.) during a twenty-four-hour period; two with venous pressures of 15 cm. recovered from their heart failure within a week; three had left-sided heart failure which rapidly disappeared. Smaller doses of lanatoside C (five to twenty tablets) were given orally to three patients with venous pressures greater than 20 cm. of saline, with favorable results. All received maintenance doses of one to five tablets a day. None of these patients exhibited signs of over-digitalization, and all showed marked improvement after receiving lanatoside C.

MAINTENANCE DOSE

It is desirable to know the maintenance dose of lanatoside C when the heart rate in cases of auricular fibrillation has dropped to about 80. We found that when the heart rate prior to treatment was very rapid and the venous pressure high, five tablets (1.25 mg., or 4.5 cat units) were usually required daily during the period of congestive failure. In two instances, it was necessary to give ten tablets a day. Once good compensation was established, however, doses of this magnitude occasionally brought about symptoms of over-digitalization, such as nausea, vomiting, and numerous extrasystoles, although these were not at all common. When such symptoms did appear, the administration of the drug was discontinued for two days, after which a daily dose of one to three tablets kept the pulse rate between 60 and 70.

For example, O. N., a 56-year-old man with advanced mitral heart disease, auricular fibrillation (rate 140), and severe congestive failure (venous pressure, 28) required 2.5 mg. (ten tablets) of lanatoside C daily during the nineteen days his venous pressure remained above 19. Smaller doses resulted in a heart rate of 100 or more, increased dyspnea, orthopnea, etc., but, when the 2.5 mg. dosage was continued for three days after the venous pressure had fallen to 8, the patient complained of nausea, emesis, and palpitation, and numerous extrasystoles were heard.

Administration of lanatoside C was discontinued for two days, and then a daily dose of two tablets kept the pulse rate between 60 and 70 and permitted moderate activity.

DURATION OF ACTION OF LANATOSIDE C

How quickly is lanatoside C destroyed in the body? No chemical means has yet been devised to solve this problem. On the other hand, the heart rate of patients with auricular fibrillation offers a reasonably reliable method of checking the drug's duration of action. Seventeen patients with heart rates of more than 120 were given lanatoside C until the rate fell to 80, or lower. The drug was then withheld, and the heart and radial pulse rates were checked daily until they rose above 90. The acceleration occurred within seven to twenty-one days, with a mean of twelve days. This variability (seven to twenty-one) can probably be explained in part by the fact that in the presence of severe congestive failure the escape of the pulse occurs more rapidly. This approximates the results reported by Robinson[11] for digitalis purpurea.

NORMAL SINUS RHYTHM

THERAPY	TOTAL NO. OF CASES	AV. NO. OF DAYS FOR VENOUS PRESSURE TO FALL TO 8 CM. WATER	AV. NO. OF DAYS FOR ONSET OF DIURESIS	AV. NO. OF DAYS FOR SIGNIFICANT RISE —30%— IN VITAL CAPACITY	AV. NO. OF DAYS IN BED	AV. NO. OF DAYS IN HOSPITAL	MORTALITY %
Venous Pressure > 15 Cm. of Water							
Control	24	14.8(14)	6.4(12)	13.0(11)	24.1(12)	27.4(13)	41.7
Lanatoside C	54	4.5(39)	3.3(31)	8.5(32)	12.2(33)	19.5(27)	25.9
Venous Pressure < 15 Cm. of Water							
Control	18	3.7(12)	3.3(11)	11.6(9)	10.3(12)	18.4(14)	22.2
Lanatoside C	11	2.1(10)	3.0(6)	6.2(6)	11.4(11)	18.8(11)	0.0
Lanatoside Delayed							
Control period	21	>17.1(16)	>17.1(16)	>17.1(16)			
After lanatoside	21	3.1(16)	3.0(13)	7.3(11)	10.4(13)	19.7(12)	23.8
VENOUS PRESSURE		AURICULAR FIBRILLATION					
>15 cm. of water	67	3.4(47)	2.3(38)	8.0(40)	15.6(34)	25.7(30)	22.4
<15 cm. of water	35	2.8(8)	2.3(13)	10.5(13)	15.2(24)	23.9(21)	11.4

Fig. 3.—This table summarizes the data on which a statistical analysis of the cases of normal sinus rhythm and auricular fibrillation was based. Numbers within parentheses indicate the total number of cases from which each average used in the statistical analysis was obtained. The average number of days is reckoned from the time of admission to the hospital in all cases except in the "lanatoside delayed" series. In the latter, the average number of days is computed from the time the administration of the drug was begun. Patients received the drug within twelve to twenty-four hours after their admission to the hospital, except in the "lanatoside delayed" series, and as noted in the text.

Patients with auricular fibrillation who received lanatoside C were usually given 1.5 grains of digitalis leaves* as a maintenance dose before

*Standardized according to the U. S. Pharmacopeia X.

leaving the hospital. In no instance did evidence of under-digitalization appear within a period of two or three weeks.

Fig. 3 records the average number of days needed for venous pressures and vital capacities to come within normal ranges, the day on which diuresis appeared, and the duration of hospitalization.

It was most interesting to study the response to lanatoside C of patients with auricular fibrillation who had venous pressures greater than 15 cm. of water. The venous pressure required an average of four days to reach normal, whereas the pulse rate fell to 80, or less, much more rapidly (within two hours when the drug was given intravenously, and twenty-four to forty-eight hours after oral administration). Similarily, the onset of diuresis lagged behind the fall in heart rate, requiring an average of three days; the vital capacity took six days to rise 30 per cent. If we compare in the same table the average number of days required to lower the venous pressure of patients with normal sinus rhythm, we find that the values are approximately the same. In other words, although the pulse rates indicate that there was an excellent digitalis response within a few hours after giving lanatoside C, the objective signs of congestive failure disappeared only a little faster when the patients had auricular fibrillation than when they had normal sinus rhythm. This is indirect proof that, if the drug is effective in relieving cardiac failure with auricular fibrillation, it is nearly as effective when the heart failure is associated with normal sinus rhythm.

USE IN CARDIAC FAILURE IN THE PRESENCE OF NORMAL SINUS RHYTHM

MacKenzie[12] and Lewis[13] have been skeptical as to the value of digitalis in the treatment of heart failure which is not associated with auricular fibrillation, although enthusiastic about its efficacy when the heart failure is associated with auricular fibrillation. They ascribe the improvement in the circulation to the slowing of the pulse rate. Many physicians have agreed with MacKenzie and Lewis, but others, led in this country by Christian,[14] have insisted that digitalis is almost as effective in the presence of normal sinus rhythm.

Peters and Visscher[15] and Moe and Visscher,[3] working with the isolated heart-lung preparation, have demonstrated beyond doubt that digitalis increases the mechanical efficiency of the failing animal heart tremendously. Anitschkow and Trendelenburg[16] found that strophanthin reduces the elevated venous pressure and increases cardiac output in animals with failing hearts, and Cohn and Steele[17] have shown that digitan has the same effect. As far as we know, there has been no clinical investigation which has demonstrated scientifically that digitalis glycosides are efficacious in the treatment of congestive heart failure associated with normal sinus rhythm.

We determined to investigate this problem by dividing cases of heart failure not associated with auricular fibrillation into two series, the cases for each series to be selected alternately. Patients in the first, or control, series were kept in bed, their fluid intake was restricted to 800 c.c. per twenty-four hours, and they received sedatives as needed, but no other medication; those in the second series were given the same treatment, with the addition of lanatoside C. There were sixty-five cases in the lanatoside series and sixty-three cases in the control series. The one deviation from the rule of alternating cases came about through the insistence of an attending physician that a patient with severe heart failure receive lanatoside C despite the fact that this patient was to have been put in the control series. Rheumatic valvular lesions, hypertension, coronary arteriosclerosis, and syphilitic heart disease were among the causes of the heart failure in these cases. Patients with heart failure caused by vitamin B deficiency and hyperthyroidism were excluded. With but few exceptions, these patients were victims of long-standing heart disease who had been treated in this hospital on one or many occasions; all had severe congestive failure and presented difficult therapeutic problems.

Lanatoside C was given in the same dose that had been used for patients with auricular fibrillation. It was planned to make daily measurements of venous pressure and vital capacity on all of the patients in each series, and this was usually carried out, but, occasionally, a resident physician failed to notify Dr. LaDue that a patient had been admitted and assigned to one or the other series, as a consequence of which daily measurements of venous pressure were not made on two patients in each series.

Elevation of venous pressure is, in our opinion, the most accurate quantitative measure of right-sided heart failure; 8 cm. of 2 per cent sodium citrate solution was regarded as normal.

The first vertical column in Fig. 3 summarizes our observations in forty-two cases in the control series and forty-nine in the lanatoside C series. There were actually sixty-three cases of heart failure in the control series and sixty-five cases in the lanatoside C series, but nineteen patients who were originally in the control series and fourteen in the lanatoside series died and were not included in the statistical studies on the rate of fall in venous pressure.

Lessening of visible edema lagged behind the fall in venous pressure and was therefore a less accurate indication of the effect of treatment. On the other hand, the onset of diuresis (as noted in Fig. 3) closely paralleled the fall in venous pressure and not infrequently occurred before the latter dropped to 17 cm., the level at which the edema tendency manifests itself when the patient is up and about. Diminution of venous pressure is not the sole factor in the production

of diuresis because change in posture (bed rest) alters the effect of gravity on capillary filtration. Restriction of salt intake (not done in our cases) also tends to facilitate diuresis, but lowering of the plasma proteins, which occurs occasionally, retards its onset. Hence diuresis is a less reliable criterion of the effectiveness of the drug than are alterations in venous pressure. The time of onset of diuresis could not be ascertained in five of the control series and twelve of the lanatoside series because of incontinence.

It is impossible to measure the pressure in the pulmonary veins of man. In our opinion, the best quantitative index of changes in the degree of failure of the left ventricle is an increase or decrease in vital capacity. Vital capacity measurements were made daily, when possible. Since the close cooperation of the patient is needed in order to secure reliable vital capacity measurements, subjective factors often preclude obtaining accurate data. It was impossible to get reliable data on vital capacity in six of the control and eleven of the lanatoside series.

We found that the difference between the two series with respect to lowering of the pulse rate was not statistically significant.

The average number of days in bed and average length of hospital stay are measures of the efficacy of a drug in the treatment of heart failure, but are subject to the judgment of the physician in attendance. Usually, patients were allowed to get up seven days after the disappearance of all signs of congestive failure, unless there was some specific contraindication. One observer was responsible for these decisions (as to when the patient might get up and go home) in most of the cases. Despite these uncontrollable aspects, a glance at Fig. 3 will show that even these data showed the same trend as the unequivocal changes in venous pressure.

The "lanatoside C delayed" portion of Fig. 3 refers to twenty-one patients who were originally in the control series for an average of seventeen days, but were then given lanatoside C because they had failed to show the slightest sign of improvement; in fact, most of them were worse than when they entered the hospital, and it appeared that they were going to die. Since, in our opinion, it had not yet been proved scientifically that a digitalis glycoside is beneficial in congestive heart failure with normal sinus rhythm in man, and inasmuch as some experienced clinicians do not give digitalis in cases of heart failure associated with normal rhythm, we felt justified in withholding lanatoside C until we had proof pro or con.

Professor Treloar, head of the division of biometrics at the University of Minnesota, aided us in analyzing our results statistically, making use of the so-called "t" test for small numbers and random sampling. The cases were divided into two groups: (1) controls and treated patients with initial venous pressures greater than 15 cm. of water, and (2) con-

trols and treated patients with initial venous pressures less than 15 cm. The following statements apply only to group 1. Statistical analysis of the changes in venous pressure shows that there is a probability of less than one in ten million that the difference would arise through chance. A probability of five, or less, in 100 is ordinarily considered significant in the application of this test, although the strictest observers accept one in 100 as demonstrating that the results are not fortuitous. We can therefore state that, in our study, the average length of time required for the venous pressure to fall to 8 cm. of water was longer in the control series (14.8 days) than in the series in which lanatoside C was given (4.5 days).

Analysis of the reliability of the data concerning relative changes in vital capacity shows that there are not more than four chances in 100 that the results were accidental. That the rise in vital capacity took 100 per cent longer in our controls therefore seems significant. The differences in the rate of onset of diuresis would occur by chance only twice in a thousand times. Diuresis appeared twice as rapidly in the lanatoside C series.

Application of the statistical "t" function to the differences in the average number of days in bed (twice as long in the control series as for treated patients) shows that the probability of such an increase through chance is only one in 1,000. Patients in the control series were confined to the hospital approximately a week longer, and there are only six chances in 1,000 that this was accidental.

Because of the small number of cases, the value of the mortality statistics may be regarded as dubious. However, it is worth noting that the mortality in the control series was always higher than among the patients who received lanatoside C. Moreover, the number of deaths among our most seriously ill patients, who were originally in the control series and were eventually given lanatoside C (the "lanatoside C delayed" series), was approximately the same as among the lanatoside-treated patients who had venous pressures above 15 cm. of water and were given the drug on admission.

If we examine the figures for the "lanatoside C delayed" group in the same table, we find that the sixteen patients who survived had been in the control series for an average of seventeen days, with venous pressures above 20 cm. of water, before lanatoside C was given. Following the administration of 8 c.c. of lanatoside C intravenously, the venous pressures fell to 8 cm. of water, or less, within an average of three days, and diuresis appeared in three days in thirteen instances. Three patients were incontinent, so that it was impossible to measure their urinary output. In eleven cases the vital capacity showed a significant rise within an average of seven days, and in five the measurements were of no value because the patients were unable to cooperate.

The reader of this paper may criticize our transferring twenty-one cases that were originally in the control series to a separate group. Our answer is that we were forced to make this selection because these patients looked as if they were going to die. Even if there had not been pressure from the visiting staff and the house staff, we would have felt compelled to give these more seriously ill patients the benefit of a digitalis glycoside. The type of selection that was carried out does not in any way nullify the proof of the efficacy of lanatoside C, because these twenty-one patients were the most refractory in the control series. They showed no signs even of beginning improvement after an average of seventeen days. If these twenty-one patients had remained in the control group, there is no question that the mortality percentage would have been much higher than it was, and, if the objective signs of heart failure in these cases had ultimately receded, the average number of days required for venous pressure to fall and vital capacity to rise would have been increased significantly. The probability that these changes were the result of chance would still be less than one in ten million for the venous pressure and less than four in one hundred for vital capacity. As it is, we did not invalidate the proof of the effectiveness of lanatoside C in heart failure associated with normal sinus rhythm, but really added to the statistical proof by showing that, when lanatoside C was given in these stubborn cases of heart failure in which there had been no signs of improvement after seventeen days without the drug, the decrease in the objective signs of heart failure was as rapid as in the cases in the original lanatoside C series.

We believe that we have proved beyond doubt that lanatoside C is almost as effective in the treatment of heart failure in the presence of normal sinus rhythm as it is when the failure is associated with auricular fibrillation.

Lanatoside C was given intravenously in about 25 per cent of the cases and by mouth in 75 per cent. Although there was no statistically significant difference in the results obtained with the two methods of administration, the subjective response occurred far more quickly after intravenous injection of the drug. For example, the pulse pressure, as measured by the sphygmomanometer, and the pulse volume, as estimated by palpation, showed an almost immediate increase in many instances. The same was true of the circulation time, as measured by the sodium cyanide method. The following case history is an illustration.

A patient who had been in the control* series for thirteen days was growing steadily worse. The venous pressure on admission was 20 cm. of water, and remained at about this level for thirteen days. On the fourteenth day, at 3:02 P.M., when 8 c.c. of lanatoside C were given intravenously, the blood pressure was 164/100; the pulse

*This case is not included in Fig. 3. The patient came in when the statistical analysis was being made.

pressure, 64; and the cyanide circulation time, 33.5 sec. At 3:32 P.M. the blood pressure was 178/86; the pulse pressure, 92; and the cyanide circulation time, 19 sec. There was, therefore, a 44 per cent rise in pulse pressure and a 44 per cent decrease in circulation time. At 4:35 P.M. the blood pressure was 196/100; the pulse pressure, 96; and the circulation time, 20.3 sec.—a 50 per cent increase in pulse pressure and a 40 per cent decrease in circulation time. Thirty minutes after injection of the drug, roentgenkymograph studies showed a 30 per cent increase in stroke output and a 12 per cent decrease in diastolic volume. On the following day, the venous pressure was 9 cm. of water, and the circulation time, 20.4 sec.

Data on circulation time and minute volume, the latter obtained by means of the roentgenkymograph, will be reported in a later paper. This investigation, although not yet ready for publication, indicates definitely that the minute output of the heart increases within thirty minutes after the intravenous injection of 8 c.c. of lanatoside C.

EFFECT OF LANATOSIDE C UPON CARDIAC ARRHYTHMIAS

The re-establishment of normal cardiac rhythm in patients with auricular fibrillation of long standing who were being treated with lanatoside C has been frequent enough to be noteworthy. We have treated, over a period of years, an unusually large number of such patients with digitalis purpurea, and we regard the establishment of normal sinus rhythm in cases of nonparoxysmal auricular fibrillation as rare. Smith[18] states that "In our experience, digitalis rarely, if ever, has restored normal cardiac rhythm." In eight of our 102 cases of nonparoxysmal auricular fibrillation, normal sinus rhythm became established spontaneously while the patients were receiving lanatoside C.

Apparently, lanatoside C is, comparatively speaking, an effective drug in the treatment of certain cardiac arrhythmias, such as paroxysmal tachycardia of supraventricular origin, auricular flutter, and paroxysmal tachycardia caused by transient attacks of auricular fibrillation.

Five patients with paroxysmal tachycardia of supraventricular origin responded promptly to the intravenous administration of 8 c.c. of lanatoside C. Normal sinus rhythm was established within five minutes in two cases, within ten minutes in another, and within two hours in two more. The effect of carotid sinus pressure and vagus stimulation was tried in each instance before the drug was given. Comparable results were reported by Wilson and Wishart,[19] who gave digitalis purpurea intravenously.

In one instance of paroxysmal tachycardia of auricular origin, associated with recent coronary thrombosis, neither lanatoside C nor quinidine was effective. The patient finally died during an attack of ventricular tachycardia ten days after lanatoside C had been discontinued.*

*We do not give any digitalis glycosides in cases of coronary thrombosis unless 3 grains of quinidine are taken at least four times daily.

Four patients with auricular flutter were treated successfully with lanatoside C. Two of them had mitral stenosis and entered the hospital with 2:1 block and ventricular rates of 188 and 167, respectively. Both received 8 c.c. of lanatoside C intravenously, and normal sinus rhythm was restored in the first case within five minutes, and in the second within eight minutes. In neither did the mechanism pass through a stage of auricular fibrillation before normal rhythm became established.

The third patient, a young girl with congenital heart disease, had had, to our knowledge, auricular flutter for more than a year. Both digitalis and quinidine were tried without success, and she was given two tablets (0.5 mg.) of lanatoside C daily. Two months later an electrocardiogram showed that normal sinus rhythm had become established.

The fourth patient, a 76-year-old man with congestive failure caused by hypertensive and arteriosclerotic heart disease, was fully digitalized on admission and had auricular flutter with a variable block of 2:1 and 3:1. On the seventh day, 1.25 mg. of lanatoside C were substituted for digitalis purpurea and thirteen days later, the flutter changed to auricular fibrillation, with a ventricular rate of 45. Because of the slow rate, the administration of lanatoside C was discontinued and six days later, three grains of quinidine were given three times daily. The next day the pulse rate rose to 90, and two tablets (0.5 mg.) of lanatoside C, plus 9 grains of quinidine, were given. Twenty-four hours later an electrocardiogram showed normal sinus rhythm. The patient was discharged, and advised to take 9 grains of quinidine and 1.5 grains of digitalis purpurea daily, but failed to do so. Within two weeks he was readmitted; he had mild heart failure and auricular flutter (ventricular rate 150, block 2:1). The following day, 8 c.c. of lanatoside C were injected, and twenty-four hours later an electrocardiogram showed normal rhythm. He left the hospital taking 9 grains of quinidine and 1.5 grains of digitalis, but three months later returned to the dispensary with auricular fibrillation.

Another patient with auricular flutter and a 2:1, 3:1 block, who did not have heart failure, was given 8 c.c. of lanatoside C, followed by three tablets daily, and on the fourth day developed auricular fibrillation. She had been treated for auricular fibrillation for two years in the outpatient department, so that quinidine was not tried.

A 67-year-old man with coronary thrombosis came into the hospital with auricular flutter (ventricular rate 164, 2:1 block). Although it is our custom to be exceedingly cautious in administering digitalis in the presence of coronary thrombosis, we considered the rapid rate a justification for giving lanatoside C. Eight c.c. were injected without effect, and the patient died on the eighth hospital day. At autopsy, a fresh thrombus was found in the anterior descending branch of the left coronary artery, with infarction; acute pancreatitis was also noted.

A 54-year-old man with lobar pneumonia (pneumococcus, type VII), involving the entire right lung, had, in addition, auricular flutter (auricular rate 375, with 2:1, 3:1 block before the administration of antipneumococcus serum). He was given 12 c.c. of lanatoside C intravenously; the apical rate was 170 at the time of the injection. An hour later it was 64, and, after twelve hours, an electrocardiogram showed normal sinus rhythm, with a rate of 150. The patient died two hours later.

Seven patients with paroxysmal auricular fibrillation of one to four days' duration were given 8 c.c. of lanatoside C intravenously. In four, normal sinus rhythm was restored within ten minutes, and, in the remainder, within twenty-four hours. Two patients had venous pressures above 15 cm. of water; in one the pressure fell from eighteen to eight in an hour, and, in the other, from sixteen to six in one and one-half hours. It is of interest that, in two of these cases, the rhythm went through a stage of auricular flutter before becoming normal. Only one patient to whom lanatoside C was given had normal sinus rhythm on admission, and then, while taking the drug, developed auricular fibrillation. This persisted for more than nine months. If we include the seven cases of paroxysmal auricular fibrillation with the eight cases of long-standing auricular fibrillation in which normal rhythm became established, fifteen patients with auricular fibrillation developed normal sinus rhythm during treatment with lanatoside C.

USE IN HYPERTHYROIDISM

We believe that lanatoside C will aid the heart in hyperthyroidism by reducing both the ventricular rate (in the presence of auricular fibrillation) and the venous pressure. Some of our patients received both lanatoside C and Lugol's solution; this made it impossible to draw any conclusions. There were, however, five patients with auricular fibrillation and hyperthyroidism who did not take Lugol's solution; their pulse rates and venous pressures fell promptly after the administration of lanatoside C. The following are brief abstracts of their case histories.

CASE 1.—A 65-year-old woman with hyperthyroidism and mitral disease (no heart failure) had a basal metabolic rate of +46 per cent and auricular fibrillation, with a ventricular rate of 120. She was fully digitalized on admission but was given 8 c.c. of lanatoside C intravenously, and, within two hours, the heart rate (in the electrocardiogram) was 80.

CASE 2.—A 70-year-old housewife with mitral stenosis, hyperthyroidism (basal metabolic rate +40 per cent), and auricular fibrillation (ventricular rate 120) was given 15 c.c. of an oral preparation of lanatoside C (0.25 mg. per cubic centimeter), followed by 1.25 mg. each succeeding day for seven days; by this time the heart rate had fallen to 76, and it was maintained between 70 and 80 until she was operated on. Her basal metabolic rate ranged between +32 and +40 per cent, and her venous pressure fell from 16 cm. of water to normal. After her thyroidectomy, normal cardiac mechanism was restored by means of quinidine.

CASE 3.—A 68-year-old woman, who was digitalized on admission, had hyperthyroidism, mitral stenosis, auricular fibrillation, and congestive heart failure. Her venous pressure was 22 cm. of water, and her heart rate, 150, when she was given 8 c.c. of lanatoside C intravenously in divided doses. Within twenty-four hours the heart rate fell to 89, and, within forty-eight hours, the venous pressure was 9 cm. of water. After she recovered from her congestive failure, her basal metabolic rate was still +30 per cent. She refused to be operated on, but, with roentgen therapy and lanatoside C, has remained comfortable.

CASE 4.—A 58-year-old woman with a basal metabolic rate of +36 per cent had auricular fibrillation (ventricular rate 150) but no heart failure. She was given 8 c.c. of lanatoside C, and, on the next day, the electrocardiogram showed normal sinus rhythm, with a ventricular rate of 100. After she had taken Lugol's solution for twelve days her basal metabolic rate fell to +4 per cent, and she made an uneventful recovery after thyroidectomy.

CASE 5.—A 63-year-old woman with a basal metabolic rate of +32 per cent and auricular fibrillation (ventricular rate 126) responded promptly to the injection of lanatoside C with a slowing of her pulse rate to 70. The administration of Lugol's solution lowered her basal metabolic rate to +9 per cent, and she recovered quickly after her thyroidectomy.

A sixth patient who failed to respond to lanatoside C was admitted in a thyroid crisis, with a temperature of 107° F. and a grossly irregular heart (rate 150). She died on the third hospital day.

TOXICITY OF LANATOSIDE C

The comparative rarity of toxic reactions to lanatoside C has been striking. Not a single patient was unable to take lanatoside C, and only eight patients among the 256 who were given the drug were unable to tolerate the usual doses because of intractable nausea and vomiting. However, when the drug was withheld for two days and then given in doses of one tablet (0.25 mg.) per day, these symptoms failed to recur, and the usual beneficial effect was obtained. All had extrasystoles which disappeared in two days. In only three additional patients could extrasystoles be ascribed to lanatoside C, and two of these developed a bigeminal rhythm which disappeared within forty-eight hours. These latter two patients were unable to take digitalis purpurea, but they were relieved of their heart failure when smaller amounts of lanatoside C were given.

When symptoms of overdigitalization appear following the administration of lanatoside C, withdrawal of the medication for two days seems to remove all symptoms and signs of overdosage. In our experience, four to eight days elapse before these evidences of overdigitalization disappear when they are produced by digitalis purpurea. Complete heart block in the presence of auricular fibrillation occurred in the case of a woman with arteriosclerotic heart disease who had received five tablets (1.25 mg.) of lanatoside C daily for ten days. The block disappeared thirty-six hours after the administration of lanatoside C was discontinued and failed to recur when smaller doses were given.

In ten cases, nausea and occasional emesis occurred, but, despite these symptoms, the administration of the drug was continued in the same dosage (in most instances five tablets per day), and, to our surprise, both the nausea and vomiting disappeared. Transient nausea of this type has been noticed by Visscher[20] in dogs. We have never seen evidence of mental or visual disturbance as a result of giving lanatoside C.

Four patients who could not tolerate digitalis purpurea because of nausea, emesis, extrasystoles, and rhythmic bigeminy were able to take lanatoside C without distress and with great benefit. Four patients who alleged that they had never taken digitalis were given 8 c.c. of lanatoside C intravenously on admission, with only transient nausea, and, on the following day, we discovered that they had been fully digitalized on entry.

SUMMARY

1. Lanatoside C, which is a stable, crystalline glycoside derived from digitalis lanata, caused no anatomic changes in the heart muscle of the dog when it was given in therapeutic doses daily for a period of three months.

2. Lanatoside C, when administered intravenously to patients with auricular fibrillation, reduces the heart rate to normal within a period of two minutes to two hours. When administered orally, lanatoside C reduces the rate of the heart to normal within twenty-four to forty-eight hours.

3. Lanatoside C is efficacious in the treatment of congestive heart failure when normal sinus rhythm is present. In fact, the efficacy of lanatoside C in the presence of normal sinus rhythm is almost as great as when the heart failure is associated with auricular fibrillation.

4. Lanatoside C will often restore normal rhythm in cases of supraventricular paroxysmal tachycardia and auricular flutter. In eight of our 102 cases of nonparoxysmal auricular fibrillation, normal sinus rhythm became established spontaneously during treatment with lanatoside C.

5. Lanatoside C will reduce the pulse rate to normal in some cases of auricular fibrillation associated with hyperthyroidism, and, in at least one case, the venous pressure was brought down from 22 cm. of water to 9 cm. of water within forty-eight hours.

6. Lanatoside C seems definitely less toxic than preparations of digitalis purpurea. Some patients who cannot tolerate digitalis purpurea can take lanatoside C in sufficient doses to aid in the relief of their heart failure.

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CALIBRATED PHONOCARDIOGRAPHY

A New Technique for Clinical Use

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Stockholm

THE Argentineans, Orías and Braun-Menéndez,[1] have recently published a monograph covering the most important methodologic and clinical results of phonocardiographic research. It is evident that, until the present time, most attention has been given to the four heart sounds. The third heart sound and the auricular sound, or the fourth heart sound as it is also called, have been subjected to intensive study. The different types of gallop rhythm have led to many investigations, with results of lasting theoretical and clinical value.[1-3]

Since 1906, when Einthoven constructed the first apparatus for phonocardiography, the method has been improved step by step. Nevertheless, it still has a number of unremedied technical defects; this is one of the reasons why it has not been more generally used clinically.

Other investigators have generally used an apparatus consisting of a microphone, amplifier, and oscillograph, and have recorded the electrocardiogram simultaneously. The frequency of the heart sounds varies from about 30 to a little over 1,000 cycles per second (Fig. 2). With the customary procedure, the whole of this frequency range is reproduced on a single curve. The disadvantages of using one curve are the following:

1. The sounds with a low frequency (the first heart sound, for example) have such great amplitude that the weaker murmurs of much higher pitch and smaller amplitude are drowned out.

2. No calibration has been used. Direct measurement, either of the frequency or the intensity of the heart sounds, has not been possible.

It is true that the frequency has been studied both by mathematical calculation and by the use of filters.[4-7] On the other hand, no objective measurements of the intensity have been made.

The intensity of murmurs has always been considered important in daily clinical practice. Levine,[8] for example, grades the systolic murmurs into "very slight," "slight," "moderate," "loud," "very loud," and "loudest possible." But, to quote Orías and Braun-Menéndez,[1] "we have to rely almost entirely on the results of auscultation. No objective studies have been made of the absolute intensity of murmurs."

From the Pediatric Clinic, Kronprinsessan Lovisas Vårdanstalt, Stockholm (Professor A. Lichtenstein).

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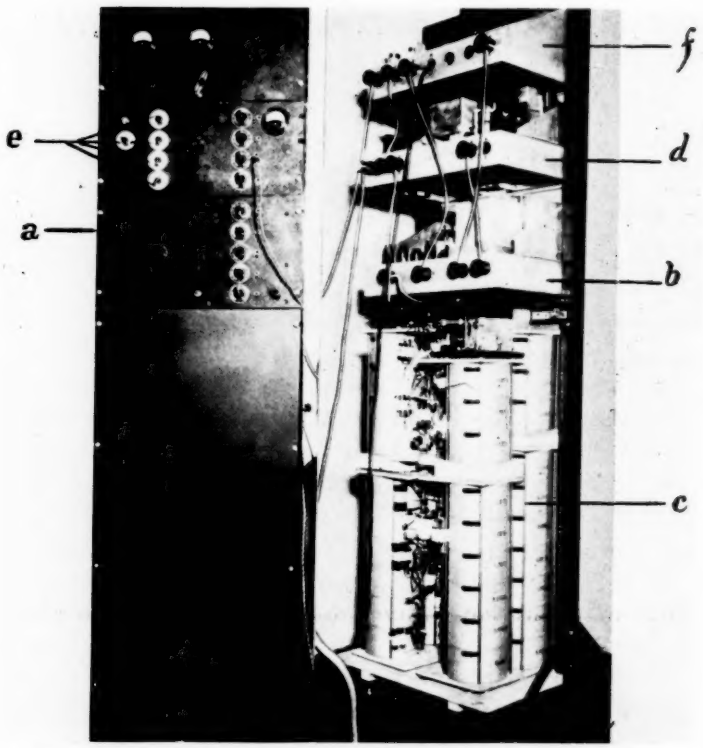


Fig. 1.—The phonocardiograph, seen from front and rear; *a*, input of the apparatus; *b*, first amplifier; *c*, filter system; *d*, second amplifier; *e*, control switches for the voltage dividers from the tube oscillators; *f*, voltage apparatus.

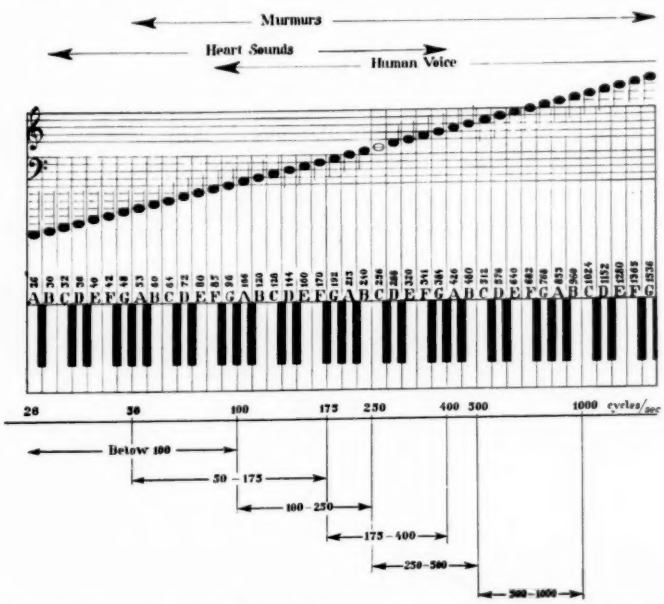


Fig. 2.—The position of the different frequency ranges (band-pass filters) in the musical scale. All figures denote cycles per second.

Consequently, there is need of a method which will register the intensity of all sounds produced by the heart.

I shall now describe a phonocardiograph which I have constructed in collaboration with Mr. Torkel Stordal, an electrical engineer.

METHOD

The apparatus is made up of three main components:

1. A microphone of the crystal type.*
2. A phonocardiograph (Fig. 1).
3. An electrocardiograph of the three-lead type† (Fig. 3).

The impulses are conducted from the microphone to the input of the phonocardiograph (*a*, in Fig. 1). Then they enter the first amplifier (*b*, in Fig. 1), where they are distributed into four channels, each of which contains an independent amplifier. On leaving the first amplifier, the impulses are led to a filter system (*c*, in Fig. 1).

Filter System (*c*, in Fig. 1).—Two types of filters are used, namely, high-pass filters which exclude the low frequencies but permit the passage of high ones, and low-pass filters which have the opposite effect. It is very important that the filters be highly selective, and this we have accomplished by means of special coils. With these filters, the whole of the frequency range covered by the heart sounds is divided into a series of separate frequency bands.

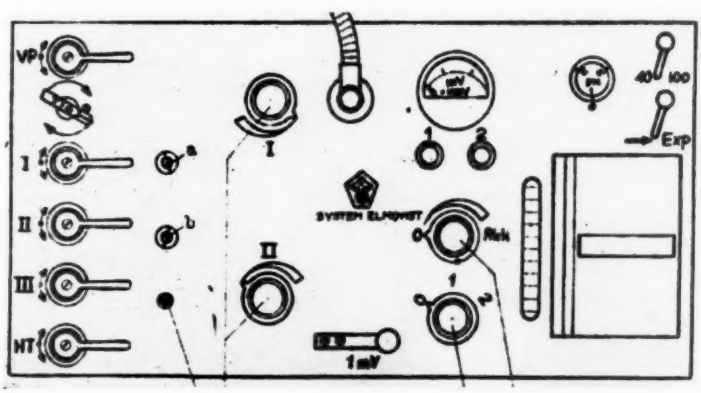


Fig. 3.—The manipulating board of the electrocardiograph.

Fig. 2 shows the distribution of the different frequency ranges in the musical scale. As will be seen, the band-pass filters are six in number. The first five overlap one another because it was found that otherwise the frequency ranges were so narrow that interference phenomena developed. As mentioned, the phonocardiograph has four independent channels, with built-in amplifying systems. By means of a switch, two of the channels are alternately connected with two different band-pass filters. From the filter units the impulses are led to the second amplifier (*d*, in Fig. 1) of the phonocardiograph, and thence to the moving-coil oscillograph. The moving coils, which are placed in the electrocardiograph, are manipulated by means of five handles (seen at the far left in Fig. 3).

*Model 66, manufactured by Shure Brothers, Chicago, U. S. A.

†"Triplex," manufactured by the Instrument Laboratory of the University of Lund, Sweden.

The switching arrangement allows one to record (1) three electrocardiographic leads, together with two frequency ranges, or (2) only Lead II of the electrocardiogram and the four remaining frequency ranges. Thus, for every patient, two records are required, as follows:

PCG, Phonocardiogram; ECG, Electrocardiogram.

A.
- PCG below 100 cycles/sec.
- ECG Lead I.
- ECG Lead II.
- ECG Lead III.
- PCG 500 to 1000 cycles/sec.

B.
- PCG 50 to 175 cycles/sec.
- PCG 100 to 250 cycles/sec.
- ECG Lead II.
- PCG 175 to 400 cycles/sec.
- PCG 250 to 500 cycles/sec.

Calibration of Intensity.—In addition to the amplification and filter apparatus just described, an apparatus for calibration of the amplitude of the sounds is also built into the phonocardiograph. It consists of tube oscillators which deliver tones of a known pitch and amplitude. These oscillators are placed far to the left in the second amplifier (*d*, in Fig. 1). The tones emitted have frequencies of 70, 175, 275, 375, and 700 cycles per second. The tone 70 lies both within the band below 100 cycles and in the 50- to 175-cycle band. The other tones fall into the middle of their frequency ranges. By means of voltage dividers (consisting of a tapped resistance), it is possible to reduce the full voltage sent out in the tube

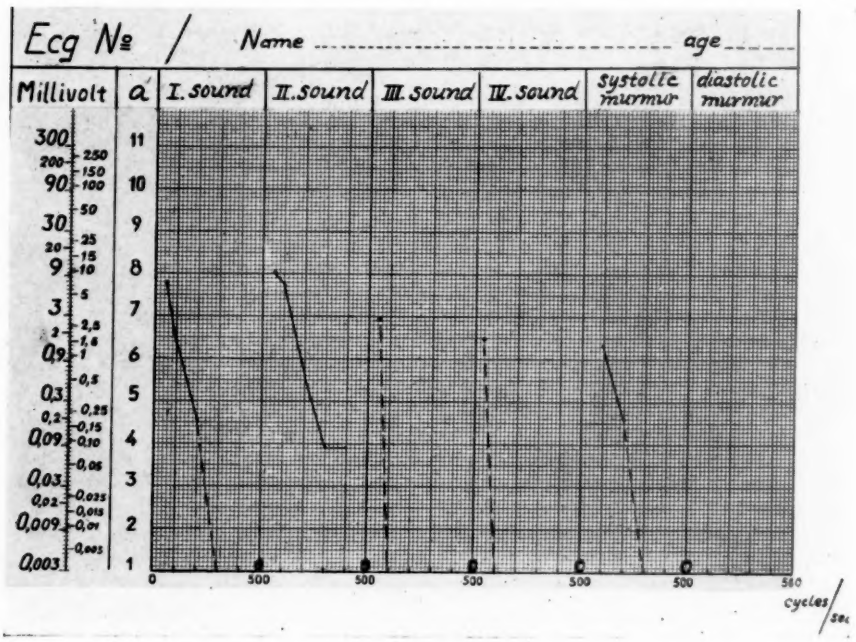
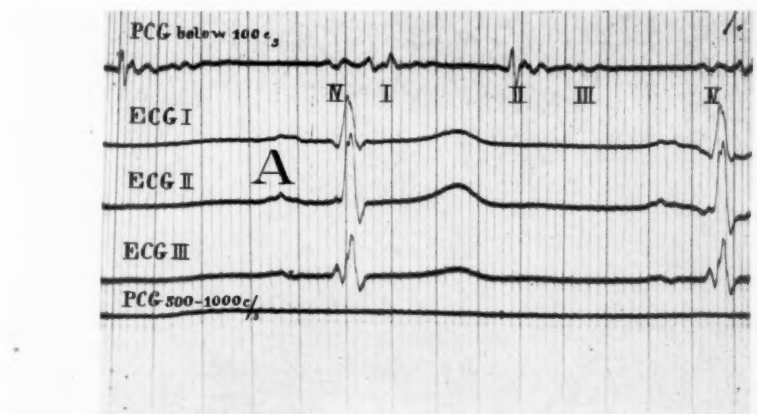


Fig. 4.—Diagram of calibrated phonocardiography (Case 2, Fig. 6). *Abscissa:* the different frequency ranges in cycles per second. *Ordinate:* the amplitudes (voltages) of the sounds. Logarithmic scale in millivolts from the microphone. Under *a* are given the voltage divider positions (see text and *e* in Fig. 1).

oscillators. Thus, in every case, the voltage of the impulses coming in from the microphone can be compared with the calibration voltage. The latter is measured in millivolts, within the limits of 0.003 to 300 millivolts. The absolute number of millivolts, accordingly, is dependent upon the microphone, and, therefore, every apparatus must be adjusted, unless it is possible to obtain microphones with exactly the same physical characteristics.

Graphic Registration.—The results are recorded in a coordinate system, as is seen in Fig. 4. The first, second, third, and fourth heart sounds, and the systolic and diastolic murmurs are placed in sequence along the abscissae of the phonocardiogram, each one in a separate part. The different frequency ranges are measured in cycles per second. The intensity of the different sounds, in millivolts, according to a logarithmic scale, is recorded along the ordinates. With printed charts of this kind, it takes little time to draw the curves. Fig. 4 is the graph obtained in Case 2 (see later). The following general facts emerge from



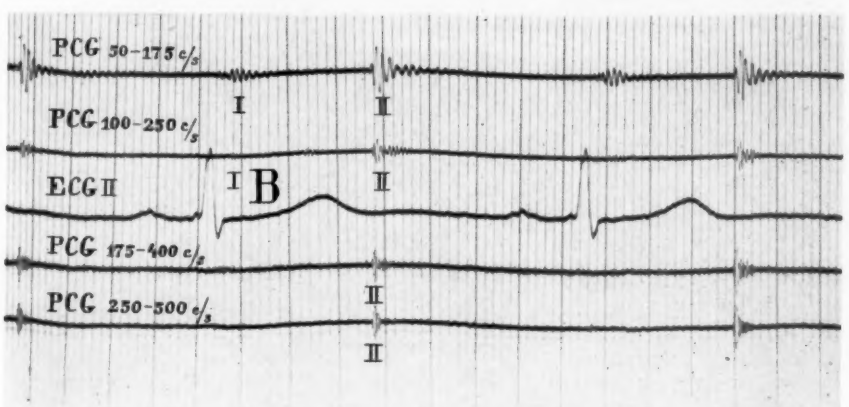


Fig. 5.—Case 1. *A* is first record, and *B*, second record (see p. 157). *PCG*, Phonocardiogram; *ECG*, electrocardiogram; *I*, first heart sound; *II*, second heart sound; *III*, third heart sound; *IV*, auricular, or fourth, heart sound; *S.M.*, systolic murmur; *P.D.M.*, protodiastolic murmur; *P.M.*, presystolic murmur; *C.M.*, continuous murmur.

consideration of the different curves in this figure: The greatest amplitude of the first and second heart sounds is below 100 cycles per second, and this amplitude decreases rapidly with increasing frequency. The first sound, especially, has relatively few overtones, whereas the overtones of the second sound continue up to 500 cycles per second. The third and fourth heart sounds are registered only in the frequency range below 100 cycles. The accidental systolic murmur is registered in the 50- to 175-cycle range, where it has an amplitude of about 1.5 millivolts, and in the 100- to 250-cycle range, where it has an amplitude of 0.18 millivolt. The curves also illustrate the well-known fact that the ear is relatively much less sensitive to low than to high tones. The third and fourth sounds, which have low frequencies and no overtones, have a much greater amplitude than the slight systolic murmur. Yet the ear cannot perceive these sounds, although the much weaker accidental murmur of higher pitch can be

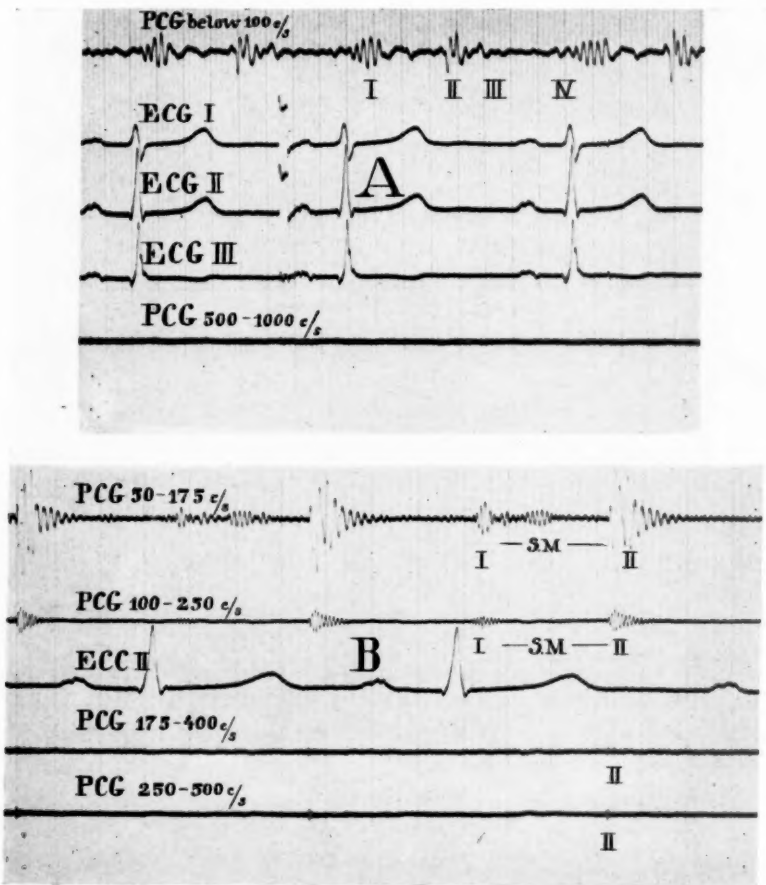


Fig. 6.—Case 2. For explanation of signs see Fig. 5.

heard without difficulty. Furthermore, the diagram shows the great differences in degree of amplification in the different frequency ranges. In the 250- to 500-cycle frequency range, the amplification in this case was about one hundred times as great as in the range below 100 cycles per second. This is particularly evident from the graph of the second heart sound.

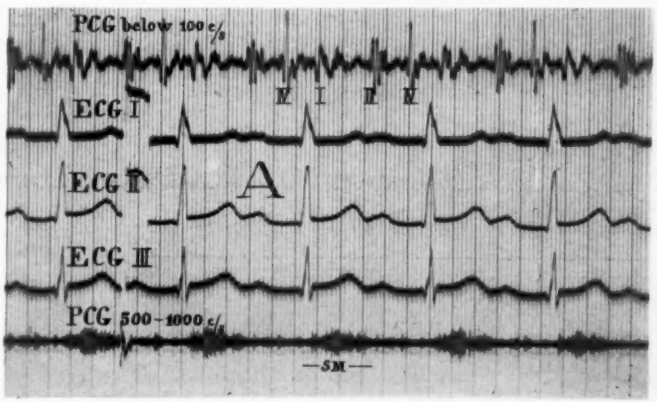
CASE REPORTS

CASE 1 (Fig. 5), *Normal.*—The patient was a boy, 7 years old, with no signs of cardiac disease.

Physical examination revealed pure heart sounds.

The electrocardiogram was normal.

Phonocardiogram.—All of the four heart sounds were registered, the first up to 250 cycles per second, and the second, with its overtones, up to 500 cycles per second. There were no murmurs.



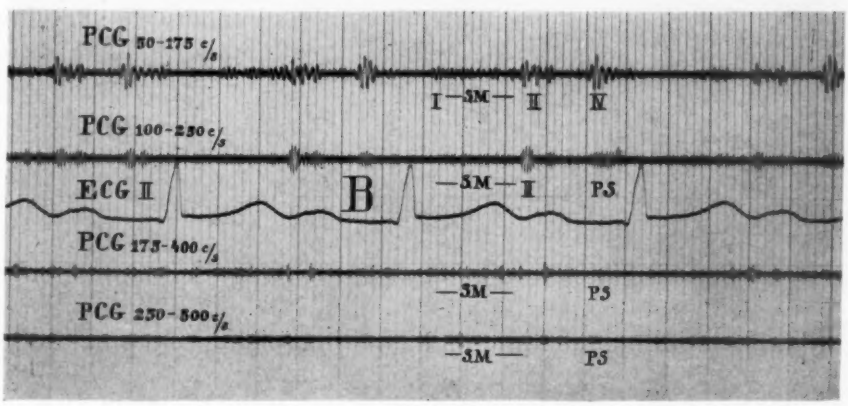


Fig. 7.—Case 3. *ECG* and *PCG* taken May 17, 1939. For explanation of signs see Fig. 5.

CASE 2 (Figs. 4 and 6), *Probably Accidental Systolic Murmur.*—The patient was a healthy 10-year-old girl who had been previously unaware of any heart defect.

Physical examination revealed a faint systolic murmur, maximal over the apex and slightly fainter in the sitting position.

The electrocardiogram showed a P-Q interval of 0.17 sec., a normal QRS complex, with no axis deviation, a weakly diphasic T_3, and normal S-T segments.

Phonocardiogram.—All four heart sounds were registered. A faint systolic murmur (S.M.) was registered in the 50- to 175- and 100- to 250-cycle ranges. For the graphic registration, see under Graphic Registration and Fig. 4.

CASE 3 (Figs. 7 and 8), *Rheumatic Pancarditis, With Mitral Defect.*—A girl, R. J., aged 11 years, had a typical history of joint manifestations and high fever of long duration. Pallor and slight dyspnea were present.

Physical examination (May 17, 1939) showed great enlargement of the heart. The left border was located at the anterior axillary line, and the right, 2 cm. beyond the right sternal border. Agitated heart action and palpitation were observed, and there was a distinct gallop rhythm over the apex which lifted the stethoscope in time with it. There was a hissing, musical systolic murmur over the apex, as well as a short presystolic murmur.

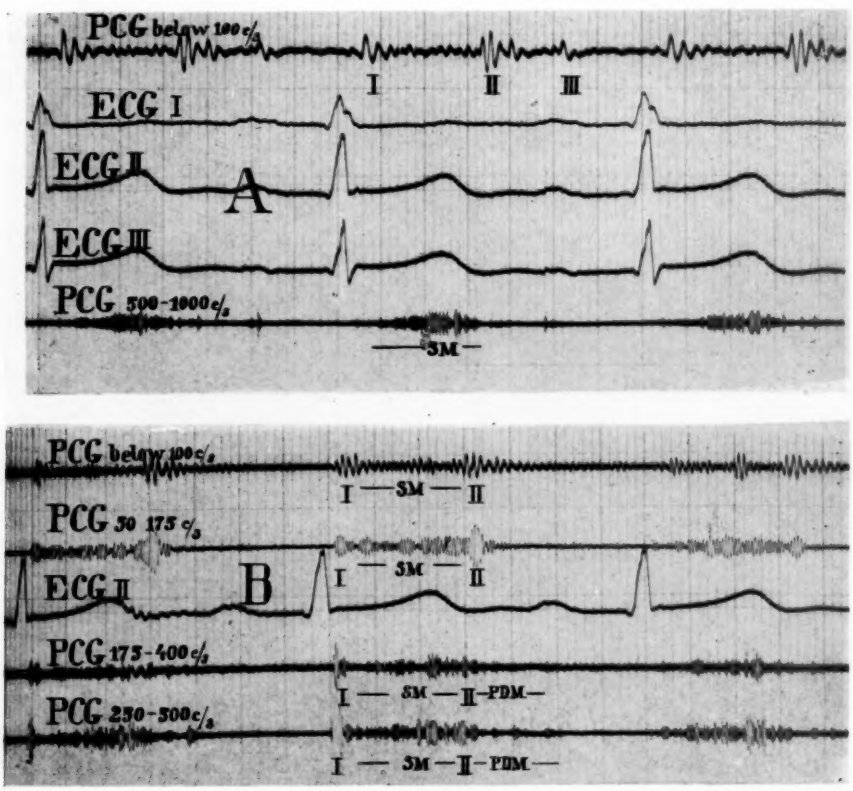


Fig. 8.—Case 3. *ECG* and *PCG* taken Feb. 6, 1940. For explanation of signs see Fig. 5.

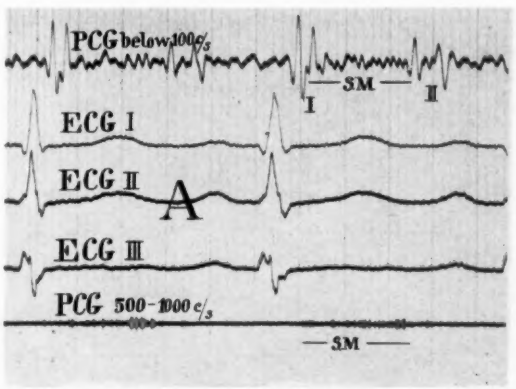
Roentgenologic examination showed a greatly enlarged heart, with a mitral configuration.

The electrocardiogram showed normal sinus rhythm, a rate of 110 beats per minute, partial A-V block, with prolongation of the P-Q interval to 0.26 sec., distinctly elevated S-T segments in Leads II and III, and broad P waves, lasting 0.11 sec.

Phonocardiogram.—Under 100 cycles per second, an extremely powerful auricular sound, with a greater amplitude than the first and second heart sounds, was registered. The overtones of the fourth sound could be followed up to 500 cycles per second and corresponded to the presystolic murmur (P.S.). There was a systolic murmur of high frequency which had its greatest amplitude between 500 and 1,000 cycles per second (S.M.).

Examination on Feb. 6, 1940, showed improvement in the general condition and fairly good compensation. The patient was out of bed several hours every day, but the slighest exertion made her short of breath and tired.

Physical examination showed that the right and left borders of the heart were located 3 cm. beyond the left mammillary line and 2 cm. beyond the right sternal border, respectively. Palpitation was still present. The presystolic murmur had disappeared, but there was still a long, hissing, musical systolic murmur of maximal intensity over the apex.



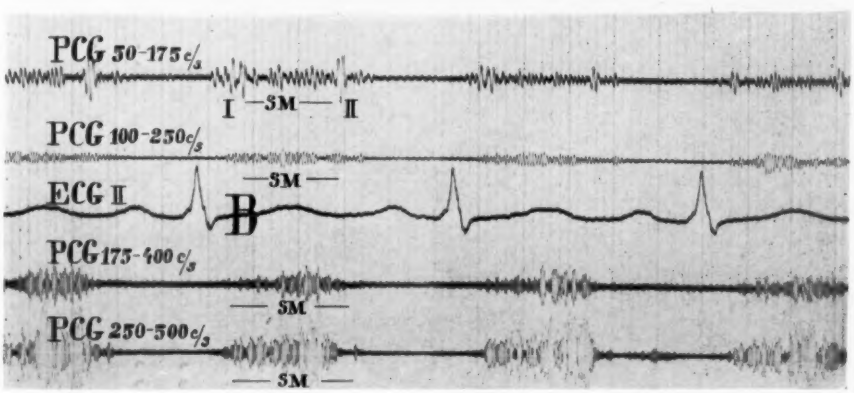


Fig. 9.—Case 4. For explanation of signs see Fig. 5.

Electrocardiographic examination showed that the heart rate had slowed to about 95 beats per minute. The electrical axis lay somewhat farther to the right. The P-Q interval of 0.25 sec. showed that partial block was still present. The P waves were broader, measuring 0.12 sec. There was still an elevation of the S-T segments in Leads II and III.

Phonocardiogram.—The powerful auricular sound had disappeared, as had the presystolic murmur. The third sound was distinct. A powerful systolic murmur of 50 to 1,000 cycles per second was registered.

Epicrisis: This case was that of an eleven-year-old girl with rheumatic pancarditis and mitral stenosis. Electrocardiograms showed partial A-V block, changes in the S-T segments, and broad P waves. On the first examination, phonocardiograms showed an auricular gallop and a presystolic murmur. These phenomena disappeared when the patient grew better, but a drawn-out, musical systolic murmur remained.

CASE 4 (Fig. 9), *Congenital Heart Defect.*—The patient, G. S., was a girl, aged 2 years and 1 month. The defect was detected when she was 6 months old. There were no signs of cardiac insufficiency. At birth she weighed 3,545 Gm., and, on admission, 12.4 kg. Her general condition was good, and she showed no cyanosis.

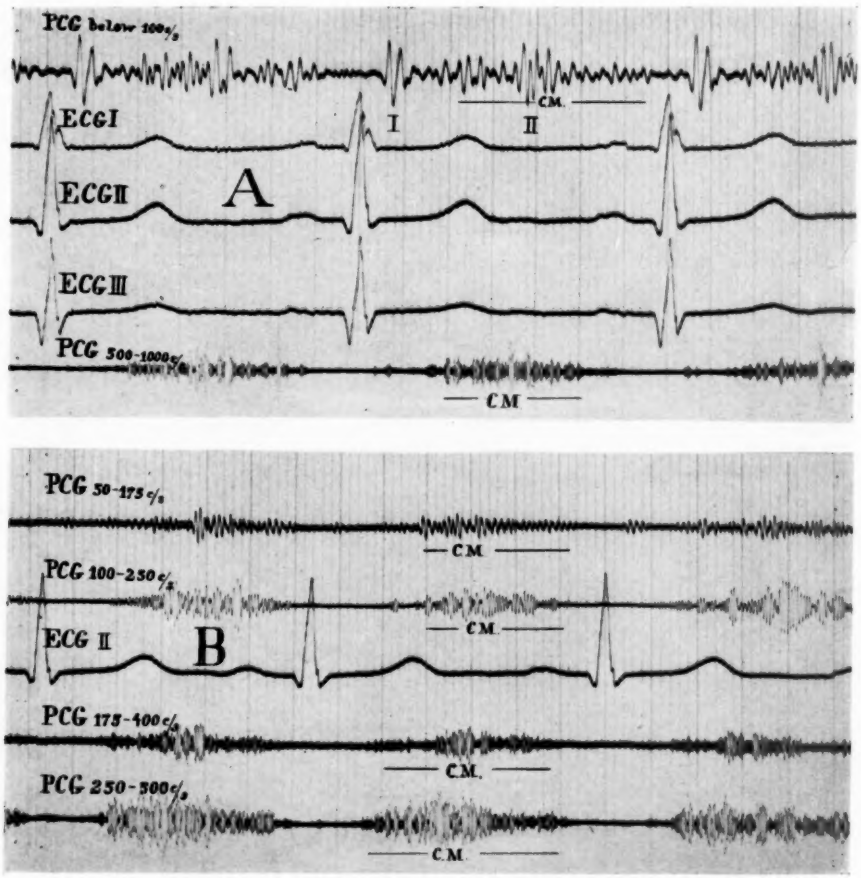


Fig. 10.—Case 5. For explanation of signs see Fig. 5.

Physical examination disclosed no enlargement of the heart, but a loud, long systolic murmur was heard over the whole cardiac region; it was of maximal intensity in the second intercostal space to the left of the sternum.

Roentgenographic examination showed slight enlargement of the heart to the left.

The electrocardiogram showed an insignificant sinus arrhythmia, a rate of 100 to 110 beats per minute, a large S_3, left axis deviation (+10 degrees), and a P-Q interval of 0.15 sec. The T waves were positive in all leads.

Phonocardiogram.—The second sound was split. There was a powerful systolic murmur between 50 and 1,000 cycles per second.

CASE 5 (Fig. 10), *Congenital Heart Defect* (probably patent ductus arteriosus).—R. T., a girl, aged 6 years and 3 months, had a congenital defect which was discovered when she was 4 months old. She was pale and thin. No cyanosis or symptoms of cardiac insufficiency were observed.

Physical examination revealed a loud systolic thrill. The right and left borders of the heart were located 2 cm. beyond the left mammillary line and 2 cm. beyond the right sternal border, respectively. There was a harsh, loud, rumbling, continuous murmur which was partly systolic and partly diastolic; it was of maximal intensity over the second intercostal space to the left of the sternum.

Roentgenographic examination showed that the heart was enlarged to the left and posteriorly.

The electrocardiogram exhibited sinus rhythm, with a rate of about 90 beats per minute. The voltage of the QRS complex was slightly high, but the complex was otherwise normal, with no axis deviation. The P-Q interval was 0.14 sec. The T waves and S-T segments were normal.

Phonocardiogram.—The frequency of the heart sounds was below 100 cycles per second. The record was dominated by the unusually loud, long, continuous murmur which lasted from the middle of systole to the end of diastole; it had a large amplitude and a frequency of 50 to 1,000 cycles per second.

The fact that the murmur was continuous suggested the possibility of patency of the ductus arteriosus.

SUMMARY

A new phonocardiographic technique is described; it has the following advantages over the previous methods:

1. The whole frequency range covered by the heart sounds is divided by filters into six frequency ranges. These six ranges are registered simultaneously. Each range can be amplified independently and to different degrees, if desired. Thus the heart sounds, with their relatively low frequency and large amplitude, are amplified only slightly in comparison to their overtones and any murmurs which may be present. The low-frequency ranges, particularly the range below 100 cycles per second, are reserved for the heart sounds, while the higher ranges reproduce the overtones of the heart sounds and any murmurs which may be present.

2. In order to register weaker murmurs accurately, disturbances from both inside and outside the apparatus are eliminated as much as possible by means of the filters.

3. By simultaneous calibration of the amplitude of the sound waves, that is, measuring the degree of amplification in each separate frequency range, data are also obtained on the intensity of the sounds.

4. Calibrated phonocardiography, which has so far been used only on children, gives promise of being a valuable diagnostic aid in practical clinical work, especially in differentiating between the murmurs associated with organic heart defects and those of a "functional" nature. Because the method permits exact measurement of all heart

sound phenomena, it should be used to complement auscultation, in order to minimize the personal factor in this important part of the physical examination.

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HEMOPTYSIS IN RHEUMATIC HEART DISEASE

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HEMOPTYSIS has long been recognized as a complication of rheumatic heart disease. The discussion of the subject in medical journals and standard textbooks of cardiology, however, gives little indication of its great incidence or importance.[1-11] In spite of its frequency and, in some cases, rapidly fatal consequences, the mechanism which produces the hemorrhage is often obscure, and treatment in severe cases is unsatisfactory or nonexistent. It seemed desirable, therefore, to investigate certain aspects of this complication of rheumatic heart disease, and the present paper deals with a preliminary study of the subject.

Five hundred twenty-one patients with rheumatic heart disease were admitted to the Beth Israel Hospital between 1928 and 1937, inclusive, and, of these, fifty had hemoptysis* prior to admission or during their hospital stay, which is an incidence of 9.5 per cent. The symptoms which were associated with the hemoptysis varied a great deal; some patients had none, but others complained of pain in the chest, palpitation, dyspnea, cyanosis, wheezing, acute pulmonary edema, weakness, faintness, and collapse. The most common symptoms were palpitation, pain in the chest, and dyspnea. Some patients showed cyanosis and acute pulmonary edema.

The average age at the onset of hemoptysis was 33.4 years; the youngest patient was 14, and the oldest, 54 years old.

I. ANATOMIC, PATHOLOGIC, AND PHYSIOLOGIC ABNORMALITIES ASSOCIATED WITH HEMOPTYSIS

As stated above, the mechanism which produces hemorrhage in cases of rheumatic heart disease is often obscure. Predisposing factors were conspicuously absent; an acute upper respiratory infection preceded the hemoptysis in three cases, and in two others the hemorrhage occurred during pregnancy. In one case the hemoptysis always followed severe exertion. There was no evidence that any of our patients had a hemorrhagic diathesis. The rheumatic infection was active in twelve of the fifty cases, but in many instances this diagnosis was not made until postmortem examination disclosed acute valvular changes. Six patients had cerebral, renal, or axial embolism, but not necessarily at the time of hemoptysis, and in not all of these cases was pulmonary infarction the cause of the hemorrhage. Thrombi were found in the left auricle in

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*Only patients who had frank hemorrhage were selected; those whose sputum was merely bloodstreaked were excluded.

one case, and in the right auricle in three others. Sclerosis of the pulmonary vascular tree was mentioned in the pathology protocols in six cases, which is an incidence of 36 per cent of the autopsy cases. Since this pathologic process was not investigated specifically, it is probable that many more patients had lesser degrees of pulmonary vascular sclerosis, and that 36 per cent represents the incidence of advanced and easily recognizable vascular disease.

Two patients had subacute bacterial endocarditis; one had a lung abscess; and two had bronchiectasis.

Abnormalities in the Cardiac Mechanism.—Twenty of the fifty patients had chronic auricular fibrillation; three had paroxysmal auricular fibrillation; and one had paroxysmal auricular flutter. The only case in the entire series in which there was a clear relationship between disordered mechanism of the heartbeat and hemoptysis was one in which the hemorrhage occurred during an attack of paroxysmal auricular tachycardia. The possibility of this relationship, however, cannot be excluded in the other cases of paroxysmal arrhythmia.

Heart Size and Valve Involvement.—All patients with hemoptysis had mitral stenosis* except one, and he had aortic insufficiency. In this case the hemorrhage was caused by a lung abscess. Twenty-seven of the patients had mitral stenosis as the only valve lesion, while the remaining twenty-two had, in addition, aortic, and, in three cases, tricuspid valve disease.

Nineteen, or 38 per cent, of the entire group had markedly enlarged hearts; sixteen had slight to moderate cardiac enlargement; and in nine cases there was no demonstrable enlargement of the heart. The size of the heart was unknown in four cases; two patients with subacute bacterial endocarditis were not included in this classification. The size of the heart was ascertained at autopsy in sixteen cases, and, in many of the remaining ones, by teleroentgenograms.

Congestive Failure and Pulmonary Infarction.—Only eight of the fifty patients had recognizable congestive failure† prior to, or at the time of, the initial hemoptysis, whereas pulmonary infarction was present in twenty-three cases, in thirteen of which there was autopsy confirmation. Of the total number of eight patients with congestive failure at the time of the initial hemoptysis, seven had pulmonary infarction. Seven additional patients whose hemoptysis was associated with pulmonary infarction developed congestive failure at varying intervals after the hemoptysis.

II. MECHANISM OF HEMOPTYSIS

In attempting to arrive at some understanding of the mechanism underlying hemoptysis in rheumatic heart disease, three facts stand

*The diagnosis of mitral stenosis was questionable in two cases.

†I.e., abnormally high venous pressure, enlargement of the liver, edema, and accumulation of fluid in serous cavities.

out above all others; mitral stenosis was present in every case (except one, in which the hemorrhage was caused by a lung abscess), pulmonary infarction was diagnosed in twenty-three cases, and, prior to the onset of hemoptysis, congestive failure was present in only eight cases.

In twenty-three, or almost half of the series, the hemorrhage was accounted for by pulmonary infarction, which is a recognized cause of hemoptysis. Pulmonary infarction may result from embolism (the source may be right auricular thrombi or peripheral venous thrombosis), or from pulmonary thrombosis, which is favored by pulmonary arteriosclerosis, congestive failure, or both. It is noteworthy that pulmonary infarction was found in seven of the eight cases of congestive failure and in only two of the nine cases in which the size of the heart was normal. Following the initial hemoptysis in the latter two cases, the size of the heart increased progressively over a period of many months, and, at post-mortem examination in one of them, marked pulmonary arteriosclerosis and multiple thrombosis were found. Therefore, pulmonary infarction is the most likely cause of hemoptysis in the presence of congestive failure, but may be excluded if the patient has no cardiac enlargement. If, however, pulmonary infarction occurs when the patient has no cardiac enlargement, and particularly if hemoptysis is followed by a progressive increase in the size of the heart, a severe degree of pulmonary arteriosclerosis may be the underlying cause.

In most of the remaining cases the hemoptysis was caused, undoubtedly, by mitral stenosis alone, without gross evidence of congestive failure, i.e., by a forceful right ventricle, mitral obstruction, pulmonary hypertension, and arteriosclerosis. McGinn and White[12] have explained the occurrence of acute pulmonary congestion and cardiac asthma in cases of mitral stenosis by stating that when the heart is speeded up by effort, excitement, or paroxysmal tachycardia, the strong, enlarged right ventricle expels more blood into the pulmonary circulation than can be passed through the stenosed mitral valve in the same unit of time. Stewart,[10] in discussing hemoptysis in three cases of mitral stenosis, came to the same conclusions regarding its mechanism. It is likely that the occurrence of hemorrhage depends not only on the degree of congestion and the height of the pulmonary pressure, but also on the presence of sclerosed vessels which rupture under the strain of congestion and hypertension (pulmonary). Proft[13] and Oppenheimer and Schwartz[11] have discussed the possibility that diapedesis may be a cause of pulmonary hemorrhage, but this view is not justified by the available facts.

Finally, hemorrhage may be caused by active rheumatic infection. Brenner[8] states that rheumatic infection of the pulmonary arteries is common, and that involvement of capillaries and venules may be the cause of hemoptysis early in the disease. There was evidence of active rheumatism in twelve of our cases. In two of the three cases in which

death occurred within one or two days, the diagnosis was made clinically, and, at post-mortem examination, in all three. The possibility of rheumatic infection of the pulmonary vessels, however, was not investigated.

It is, of course, necessary, when hemoptysis occurs in a case of rheumatic heart disease, to exclude intercurrent pulmonary disease as its source. All the known causes of hemoptysis must be considered. In the present series, one patient had a lung abscess, and two others had bronchiectasis.

If intercurrent pulmonary disease can be ruled out, and the patient is comparatively young, and especially if "left ventricular failure" can be excluded, it may be assumed that mitral stenosis is present. Hemoptysis in such cases may be of help in distinguishing between an Austin-Flint murmur and the murmur of aortic regurgitation, or in the diagnosis of mitral stenosis.

III. PROGNOSIS

At the time this study was completed, thirty-three, or 66 per cent, of the patients were dead; the average duration of life following the initial hemoptysis was 32.5 months. None of the common complications of rheumatic heart disease, with the exception of subacute bacterial endocarditis, has such a serious prognostic implication. Three patients died within one or two days after the onset of hemorrhage. Such sudden death from hemoptysis in young cardiacs (rheumatic) is a very dramatic, unexpected, and unpredictable event; as in these cases, the patients may have but minimal cardiac enlargement and be unburdened by failure or abnormal rhythm. Eight patients died within one month; seventeen, within a year; and twenty-one, or 42 per cent, within two years; only five patients survived their initial hemoptysis five years or longer. In the cases of fatal hemoptysis, therefore, only 15 per cent of the patients survived five years or longer, and, of the remaining cases, the average duration of life after the initial hemoptysis was less than a month in 28 per cent, a year, or less, in 60 per cent, and two years, or less, in 75 per cent.

The average length of time from the initial hemoptysis to the last follow-up examination of the seventeen patients who are still living was thirty-nine months, and, to date, only five of these have survived five years or longer.

Grant[14] has analyzed the after histories for ten years of 1,000 men suffering from heart disease. There were 433 patients with mitral stenosis, either alone or in combination with aortic regurgitation, and, of these, 166, or 38 per cent, had died in ten years, and twenty-five, or 5.9 per cent, had had hemoptysis. This contrasts, in the present series, with a mortality of 66 per cent, and an incidence of hemoptysis of 10

per cent. Grant showed, however, that the mortality among patients with greatly enlarged hearts and congestive failure was much higher than in the series as a whole; indeed, his main thesis was to demonstrate that congestive failure and marked cardiac enlargement are the two most important and serious prognostic indications. Nevertheless, it is noteworthy that, of 197 patients with uncomplicated mitral stenosis, those with the greatest degree of cardiac enlargement and congestive failure

TABLE I

DISTRIBUTION OF VARIOUS FACTORS IN PATIENTS WHO SURVIVED TWO YEARS OR LESS, AND IN THOSE WHO SURVIVED MORE THAN TWO YEARS

	20 PATIENTS WHO DIED WITHIN 2 YEARS	19 PATIENTS WHO SURVIVED MORE THAN 2 YEARS
*Heart size 0-++	9	†9
Heart size +++	11	7
Congestive failure	6	1
Over 30 years of age	10	12
Pulmonary infarcts	13	6
Hemorrhage (large)	6	7
Hemorrhage (small)	5	5
Auricular fibrillation (chronic)	9	11
Multiple valve involvement	14	5

*In all the tables 0 indicates no cardiac enlargement;
+, slight cardiac enlargement;
++, moderate cardiac enlargement;
+++, marked cardiac enlargement; and
++++, greatest cardiac enlargement.

†Nothing known about size of the hearts of three patients who survived more than two years.

TABLE II

MORTALITY AND LONGEVITY, AS RELATED TO PULMONARY INFARCTION

PULMONARY INFARCTION				NO PULMONARY INFARCTION			
23 CASES	1 YEAR	2 YEARS	MORE THAN 2 YEARS	27 CASES	1 YEAR	2 YEARS	MORE THAN 2 YEARS
18 died	13	2	3	15 died	6	1	8
5 living	1	1	3	12 living	4	2	6

TABLE III

MORTALITY AND LONGEVITY IN CASES OF MITRAL STENOSIS (NUMBER OF CASES OF PULMONARY INFARCTION IS INDICATED)

27 CASES	1 YEAR	2 YEARS	MORE THAN 2 YEARS	INFARCTION	NO INFARCTION
14 died	6	1	7	7	7
13 living	4	2	7	3	10

survived four to five years. In our series, the average length of life of the patients with mitral stenosis alone was fifty months, but only four of the twenty-seven had great enlargement of the heart. The mortality in Grant's forty-three cases of aortic stenosis and regurgitation was 65 per cent, whereas, in the present series, thirteen of the fifteen patients with this valve lesion died, a mortality of 86 per cent, and eight had marked cardiac enlargement.

TABLE IV

MORTALITY AND LONGEVITY IN CASES OF MULTIPLE VALVE INVOLVEMENT
(NUMBER OF CASES OF PULMONARY INFARCTION IS INDICATED)

22 CASES	1 YEAR	2 YEARS	MORE THAN 2 YEARS	INFARCTION	NO INFARCTION
18 died	13	2	3	11	7
4 living	1	1	2	2	2

TABLE V

MORTALITY AND LONGEVITY IN RELATION TO SIZE OF THE HEART (KNOWN IN 44 CASES; ONE CASE OF SUBACUTE BACTERIAL ENDOCARDITIS EXCLUDED), SHOWING THE DISTRIBUTION OF SINGLE OR MULTIPLE VALVE INVOLVEMENT AND PULMONARY INFARCTION

			1 YEAR	2 YEARS	3 YEARS	4 YEARS	5 YEARS OR MORE	
No enlargement								
9	died	1					1 ae	a 1 b 0 c 1
	living	8	2 a	1 a	2 a	1 ae	2 (1a, 1b)	a 7 b 1 c 1
Slight enlargement								
6	died	5	4 (2 ae, 1 be, 1 b)	0	0	0	1 be	a 2 b 3 c 4
	living	1	1 a					a 1 b 0 c 0
Moderate enlargement								
10	died	6	5 (1 a, 2 b, 2 ae)	0	0	1 be	0	a 2 b 3 c 3
	living	4	1 a	2 (1 a, 1 be)	1 a	0	0	a 3 b 1 c 1
Marked enlargement								
14	died	11	7 (1 b, 6 be)	1 ae	1 a	0	2 a	a 4 b 7 c 7
	living	3	1 be	0	0	0	2 (1 ae, 1 b)	a 1 b 2 c 2
Greatest enlargement								
5	died	4	1 be	2 (1 b, 1 be)	1 b	0	0	a 0 b 2 c 2
	living	1	0	0	0	0	1 ae	a 1 b 0 c 1

a, Single valve involvement; b, multiple valve involvement; c, pulmonary infarction.

TABLE VI

DATA IN TWELVE CASES IN WHICH DEATH OCCURRED WITHIN SIX MONTHS FOLLOWING THE ONSET OF HEMOPTYSIS

AGE (YEARS)	HEART SIZE	MITRAL STENOSIS ALONE	MITRAL STENOSIS AND AORTIC DISEASE	PULMONARY INFARCTION	CONGESTIVE FAILURE	SIZE OF HEMORRHAGE	LENGTH OF SURVIVAL AFTER FIRST HEMORRHAGE
14	++	*		*	0	unknown	2 days
21	+	*		*	0	unknown	1 day
40	++	*		0	0	copious	6 months
51	+++		*	0	0	unknown	few weeks
43	+++		*	*	0	unknown	2 weeks
43	+		*	*	0	copious	2 days
25	+++		*	0	0	unknown	6 months
21	++++		*	*	unknown	small	3 weeks
44	++		*	0	*	unknown	1 month
34	+++		*	*	0	unknown	2 months
36	++		*	0	0	small	4 weeks
42	+++		*	*	*	unknown	2 months

A complete analysis of our cases is shown in Tables I to VI, indicating the effect of various factors on prognosis. Other factors which might have influenced prognosis were negligible. There were four patients with hypertension; three of these were alive six, seven, and nine years, respectively, after the onset of hemoptysis, but the fourth died in a few weeks. A diagnosis of paroxysmal dyspnea was made in one case, and asthmatic bronchitis in another; both of these patients are still living. Acute pulmonary edema was diagnosed in two cases, and both patients are dead. Cardiac asthma was not mentioned in any case, although wheezing occurred in eight. Of these patients, four died one month, and one, two, and three years, and four are still alive one month, a few months, four years, and nine years, respectively, following the onset of hemoptysis.

It may be concluded that in cases of rheumatic heart disease in which there is no cardiac enlargement, hemoptysis, as a rule, appears to be of little or no prognostic significance. Most of these patients have a single valve lesion, namely, mitral stenosis. Half of our patients with slight cardiac enlargement died within one or two days after the onset of hemoptysis, and two-thirds died within a year. Since these deaths occurred in cases in which the prognosis was usually excellent, it is obvious that in such cases hemoptysis must be regarded as a grave prognostic indication. Among the remaining patients the mortality was higher, and the length of survival shorter, than would have been predicted on the basis of degree of cardiac enlargement and congestive failure alone. Hemoptysis, therefore, enhances the seriousness of the prognosis in this group. The mortality was higher among the patients with pulmonary infarction than in the series as a whole. The evidence indicates that hemoptysis during pregnancy is not necessarily in-

dicative of a bad prognosis, for the two pregnant women in our series were among the longest survivors.

SUMMARY

1. Fifty cases of rheumatic heart disease in which hemoptysis occurred are analyzed. This complication is encountered in at least 10 per cent of all adults with rheumatic heart disease who are admitted to a general hospital. In our series, the average age at the onset of hemoptysis was 33.4 years.

2. The symptoms most commonly associated with hemoptysis were palpitation, pain in the chest, and dyspnea.

3. The associated anatomic, pathologic, and physiologic abnormalities, in the order of their frequency, were:

(a) Mitral stenosis, in all but one case.
(b) Pulmonary infarction, in twenty-three cases.
(c) Multiple valve involvement, in twenty-two cases.
(d) Chronic auricular fibrillation, in twenty cases.
Paroxysmal arrhythmia, in five cases.
(e) Marked cardiac enlargement, in nineteen cases.
(f) Active rheumatic infection, in twelve cases.
(g) Congestive failure, in eight cases.
(h) At autopsy:
Easily recognizable pulmonary vascular sclerosis in six cases.
Right auricular thrombi in three cases.

4. The prognosis and the mechanism of hemoptysis are discussed.

5. It is noteworthy that only eight patients had congestive failure prior to, or at the time of, the initial hemoptysis, and that nine had hearts of normal size. Pulmonary infarction is the most likely cause when there is congestive failure and may be excluded when the heart is of normal size. The combination of pulmonary infarction, a heart of normal size, and progressive cardiac enlargement following hemoptysis may indicate a severe grade of pulmonary arteriosclerosis.

6. The occurrence of hemoptysis in a case of rheumatic heart disease may help in distinguishing between an Austin-Flint murmur and the murmur of aortic regurgitation, or in the diagnosis of mitral stenosis, in certain cases.

7. When hemoptysis occurs in rheumatic heart disease, only occasionally is it caused by something other than the heart disease.

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THE FORM OF THE VOLUME PULSE IN THE FINGER PAD IN HEALTH, ARTERIOSCLEROSIS, AND HYPERTENSION

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THE pulse wave in the digital vessels was first recorded by Müller and Weis,[1] who mention the similarity between the radial and digital pulse wave forms. Bonsdorff[2] appears to have been the next to study the digital pulse wave. Although he did not make a comparative study of the digital and radial pulses, his tracings indicate that the digital wave is similar to the radial tracings of others. Uehata[3] made a comparative study of the radial and digital pulse wave forms but did not describe the technique which he used. His results are at variance with other, more detailed descriptions. Greven and Federschmidt,[4] who used plethysmographs with optical recorders, studied the velocity of the pulse wave from the radial to the digital arteries, and also the contours of the waves. Matthes, Gross, and Gopfert,[5] who used a photoelectric technique, investigated the forms of the simultaneously recorded radial and digital pulse waves. Goetz[6] recorded photoelectrically the contour of the digital wave alone.

That the contour of the peripheral pulse wave undergoes alterations in various conditions, such as fever, chronic nephritis associated with elevated blood pressure, and arteriosclerosis, has been appreciated by every investigator who has recorded pulse waves and was recognized even before the waves were recorded. In a general way, the alterations which occur in the wave contour have been described. It is well known that the pulse becomes more dicrotic during fever, and that, in arteriosclerosis, the secondary waves on the catacrotic limb (see below) become obliterated, and the peak of the wave becomes rounded. Until the work of Matoba,[7-9] no systematic attempt had been made to differentiate the genesis of the arteriosclerotic, or high pressure, pulse from that of the normal pulse. Greven and Federschmidt, in their excellent article,[4] illustrated the transition of the normal pulse to the arteriosclerotic form, but did not investigate the matter further. Matthes, Gross, and Gopfert[5] found contour changes in their digital tracings, but failed to point out what relationship, if any, they observed between the tracings from subjects with abnormal, and those with normal, vascular dynamics, although they promised to develop this point in a later paper.

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Judging from these citations from the literature, from many published finger plethysmograms, and from an extensive personal experience with photoelectric plethysmography of the skin, one finds it obvious that the propagation of the pulse wave into the smallest arteries presents problems in circulatory dynamics which are worthy of systematic exploration. This paper presents data on the form of the volume pulse of the finger pad, on the time relations between the components of the pulse wave, and on the relations between these measurements and similar simultaneous observations on the radial pulse. The data were obtained on healthy subjects and also on patients with hypertension and arteriosclerosis.

The volume pulses of the finger pad and radial artery were selected for study for several reasons: (1) They lend themselves well to our plethysmographic technique. (2) Of all of the peripheral vascular areas in man, the finger vessels have been most studied. This furnishes a background of understanding which is not available in the case of such other areas as the ear, forehead, and forearm. (3) Records of the volume pulses in the ear, forehead, and nasal septum, made by ourselves and others,[5] have shown such a striking difference in form that they constitute a separate problem. It therefore seemed best to limit this study to the finger vessels and to learn what we could about them with our technique before extending the study to other, less well-understood areas.

METHODS

The volume pulses of the finger pad were recorded with photoelectric plethysmographs, the technical details of which have been previously described.[10-15] This method depends on the fact that, when a tissue is transilluminated, its opacity varies directly with its blood content. Each pulse effects a change in the blood content which depends on the capacity of the vessels, on the resistance encountered, on the degree of vasoconstriction or vasodilatation, on the elastic properties of the vessels, and possibly also on the elastic properties of the tissues surrounding the vessels. The resulting volume pulses are most conveniently recorded by the photoelectric technique. It is not known with any certainty whether there are volume pulses in the arteries, arterioles, capillaries, or veins. It is possible that looping of the small arteries with each pulse[16] may be the source of the volume changes which are recorded as volume pulses. Important as these questions may prove to be with respect to the interpretation of the data in this paper, it seems probable that, irrespective of how the volume pulses are actually generated in a small portion of tissue such as the finger pad, they do portray, among other things, small artery behavior. This interpretation is placed upon them here; it is subject to the indicated reservations, which we plan to explore later.

In recording the pulse wave in the larger arteries with the photoelectric plethysmograph, the instrument is brought into firm contact with the skin directly over the vessel. The form of the pulse wave in the larger vessels is not affected by the pressure exerted by the holder unless the pressure is excessive. The contour may be accurately recorded even when the instrument is several millimeters from the skin surface, but direct application is preferable because it reduces the possibility of motion of the area and skin in relation to the light. Motion grossly distorts the record. Its effects are easily recognized. The presence of a small volume pulse in

the skin vessels directly over the large artery does not affect the record of the larger pulse because the latter is enormously larger than the former. It takes but little practice to learn when the arterial pulsations are being recorded properly, for the pulsations decrease rapidly when the plethysmograph is placed on either side of the vessel. They are recorded easily only when the plethysmograph is directly over the vessel, unless the amplification is increased considerably. Other sources of error have been discussed elsewhere.[10, 11]

The radial and finger pad pulses were registered simultaneously by means of a constant-speed camera; a Cambridge string galvanometer and a General Electric tension galvanometer (type A1) were used as the recording instruments for the majority of the records. Both of these respond to frequencies well above the minimal level required (Wiggers[17]) to record the peripheral pulse accurately. The light beams were adjusted to eliminate parallax.

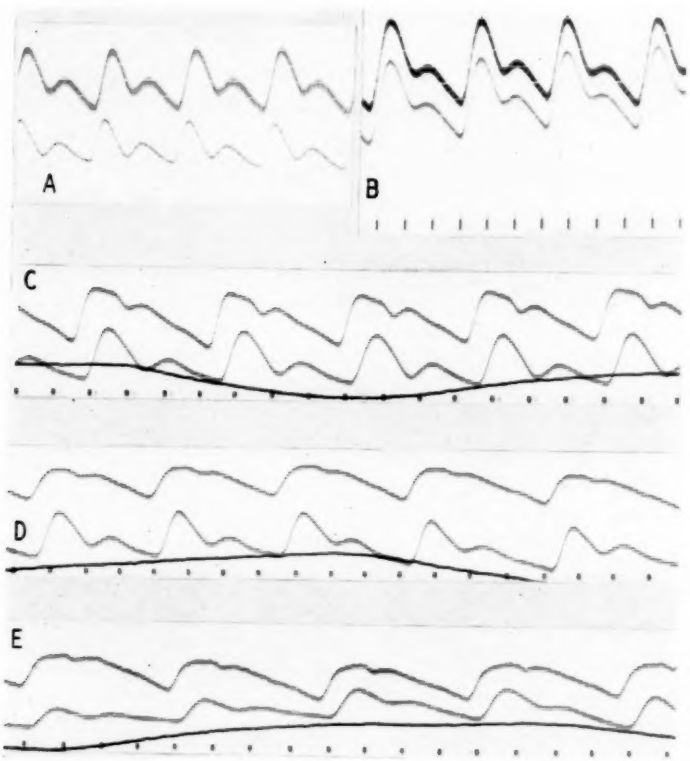

Fig. 1.—*A*, Comparison of the volume pulses of the finger pad (upper record), recorded photoelectrically, and of the terminal portion of a neighboring finger (lower record), recorded optically with a mechanical plethysmograph. Analysis of the two records by the method of Fig. 3 yields the same data; *B*, Volume pulses of thumb pad. Upper record obtained with capacity-coupled amplifier, lower record with resistance-coupled amplifier. Time, 0.2 sec.; *C-E*, Skin volume pulses. Time, 0.2 sec. Respiration (R) recorded by pneumograph. Lower volume pulse in each figure is from the finger pad. *C*, Upper record, from ear lobe; *D*, upper record, from forehead; *E*, upper record, from side of nose.

The size of the recorded pulse waves is arbitrary; it depends on the amplification employed. We used amplification sufficient to render detail apparent. It has been our practice to make the digital pulse somewhat larger than the radial.

The validity of a study of this kind depends on the adequacy of the method used. The ability of the photoelectric plethysmograph to follow vascular reactions

has been carefully compared with that of accurate mechanical plethysmographs.[11] The photoelectric records of the radial pulse are indistinguishable from those made with accepted optical methods. The accuracy of optical registration of the volume pulse of the terminal phalanx of the finger by means of a mechanical plethysmograph is theoretically open to question because of the periodicity of the system. However, such records, when properly made, compare well with the photoelectric records (Fig. 1*A*). The fact that the photoelectric technique eliminates errors caused by inertia and uses recorders of a high frequency makes it preferable to all others. In addition, this method permits flexibility in the adjustment of sensitivity without loss in frequency of response, and also allows the subject to take a natural relaxed position. The instrument is brought to the subject, not the subject to the instrument.

Since these records were made with capacity-coupled amplifiers,[14] which were used simply because they were convenient, it seemed wise to compare them with others which were made with resistance-coupled amplifiers whose adequacy had been previously established.[11, 12] Fig. 1*B* presents a comparison. The pulses were recorded with a plethysmograph specially constructed for the purpose. Two photoelectric cells were used separately and simultaneously to record the pulses in the same skin area, which was illuminated by a common light. The two records were identical.

Each subject was seated in an armchair; the right arm was comfortably flexed and placed on a support which also carried the photoelectric plethysmographs. The subject was allowed to rest for one-half hour before a record was made. Usually, two or three short records were taken at intervals of five to ten minutes. Brachial blood pressures were measured by the usual auscultatory method. Theoretical considerations indicate that it is desirable to have subjects in the basal state. However, in the case of the normal subject, the form of the finger volume pulse is not significantly different when the subject is asleep on a comfortable cot, nor is it affected by position (sitting or lying). "Crest times" (see below) remain unchanged. Also, preliminary observations indicated that variations in the tone of the finger vessels which occur as a result of "spontaneous" waves of psychic or thermoregulatory origin have little effect on the form of the volume pulse. It therefore seemed more practicable to make the observations under the conditions indicated here, with the subject in the so-called "resting" state. Most of the records were made at least two hours after eating. The room was comfortably warm (26° to 28° C.) and quiet. The subject was requested to relax as much as possible in order to minimize the influence of psychic vasomotor stimulation. The technique was explained to the subject in detail, in order to decrease the apprehension that many persons have with regard to strange procedures.

MATERIAL

The normal subjects included 115 young, healthy, male, medical students and members of the faculty; their ages ranged from 20 to 45 years. The subjects with arterial disease, who numbered forty-three, were recruited from the student body, faculty, and the vascular clinic of the Firmin Desloge Hospital. Their ages ranged from 22 to 75 years. Normal subjects were defined as obviously healthy persons whose blood pressures were less than 120/80 on several occasions, who had no demonstrable heart disease, who were normal or hypo-reactors to the Hines-Brown cold-pressor test, and who had no palpable sclerosis of the brachial artery or visible sclerosis of the retinal vessels.

No patients with aortic or mitral valve lesions were included in our series. Some of the hypertensive patients had rather severe cardiac damage, but all were ambulatory. Patients with marked disturbances in cardiac rhythm were excluded.

RESULTS

A. Normal:

Typical differences in the form of the volume pulses in several areas (forehead, side of nose, lobe of the ear, finger pad) are shown in Fig. 1*C-E*. Flattening of the summit of the primary wave and a higher position of the incisura are the main features which differentiate the volume pulses in these other areas from those in the finger pad and

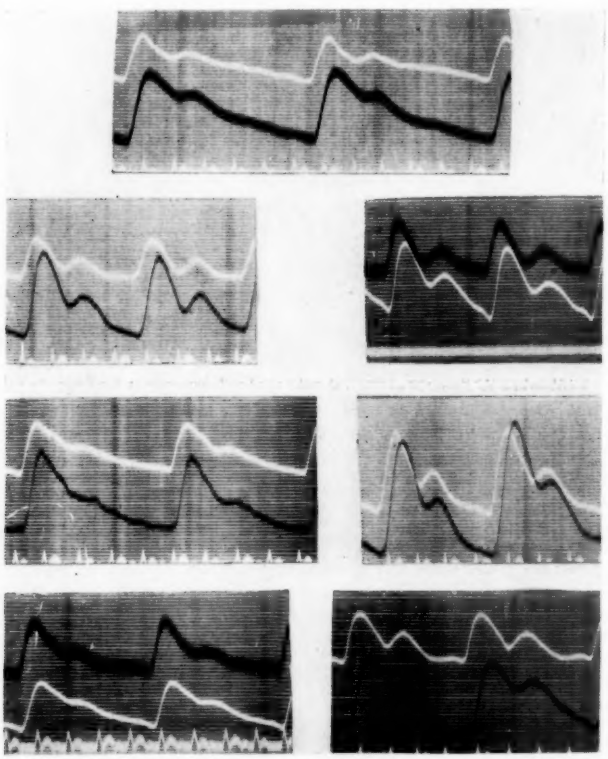

Fig. 2.—Normal finger pad and radial volume pulse tracings. Top record, radial; bottom, finger pad. Time, 0.2 sec.

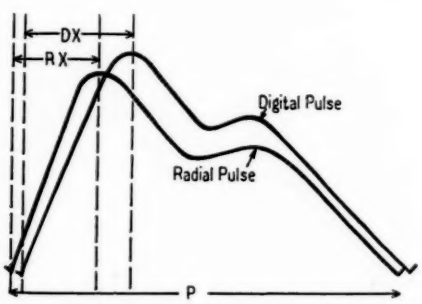

Fig. 3.—Method of analysis of the volume pulses. Primary wave is the anacrotic limb to its crest (see text for implied difficulties in ascertaining the position of the crest). DX, Digital pulse crest time; RX, radial pulse crest time; P, duration of pulse cycle.

radial artery. When crests are distinguishable, crest times are essentially the same as those of the pulse in the finger pad. Further description or analysis will not be attempted here.

It is apparent that the volume pulses of the finger pad and radial artery are grossly similar in normal subjects (Fig. 2). The method of detailed analysis of these and similar records is illustrated in Fig. 3. The method follows the procedure of Yamaguchi,[18] who calculated the duration of the ascent of the primary wave of the radial pulse in a large series of cases. He found significant differences between normal subjects and persons with hypertension and arteriosclerosis. We have called the duration of the ascent of the primary wave, the *crest time.*

TABLE I

DIGITAL AND RADIAL PULSE CREST TIMES IN NORMAL SUBJECTS

NO.	SUBJECT	AGE (YR.)	RESTING BLOOD PRESSURE	PULSE RATE	RADIAL CREST TIME IN SEC.	DIGITAL CREST TIME IN SEC.	RADIAL CREST TIME AS % OF PULSE CYCLE	DIGITAL CREST TIME AS % OF PULSE CYCLE	DIFFERENCE BETWEEN RADIAL AND DIGITAL CREST TIMES IN % OF PULSE CYCLE
1	L. S.	35	112/75	72	0.130	0.150	15.0	17.1	2.1
2	R. J.	25	110/74	85	0.112	0.130	16.0	17.8	1.8
3	R. B.	21	108/74	60	0.118	0.138	10.2	11.9	1.7
4	W. O.	24	106/75	65	0.100	0.112	11.1	12.5	1.4
5	B. M.	23	112/70	69	0.118	0.118	13.5	13.5	0.0
6	J. D.	28	112/72	86	0.112	0.120	15.3	17.1	1.8
7	A. H.	42	108/72	77	0.104	0.132	15.5	18.4	2.9
8	C. W.	23	108/70	90	0.112	0.137	13.6	16.7	3.1
9	I. E.	25	99/75	92	0.088	0.100	13.5	15.4	1.9
10	G. B.	45	112/75	68	0.102	0.125	12.0	14.3	2.3
11	V. M.	23	103/72	80	0.112	0.130	14.7	17.0	2.3
12	F. G.	24	120/80	62	0.102	0.118	10.8	12.1	1.3
13	T. K.	22	90/65	75	0.118	0.132	14.7	16.6	1.9
14	B. H.	23	112/74	71	0.105	0.125	12.4	14.8	2.4
15	J. H.	22	108/65	75	0.107	0.131	13.9	15.2	1.3
16	J. K.	22	118/68	81	0.100	0.125	13.6	15.2	1.6
17	J. A.	30	110/74	77	0.123	0.148	15.7	18.7	3.0
18	R. M.	36	105/80	77	0.123	0.142	15.6	18.4	2.8
19	E. T.	22	118/78	80	0.125	0.142	16.6	19.0	2.4
20	R. H.	24	106/75	77	0.107	0.123	13.8	15.8	2.0
21	R. G.	22	110/68	77	0.113	0.138	14.5	16.8	2.3
22	N. T.	23	110/70	86	0.100	0.119	14.3	17.0	2.7
23	N. R.	24	110/70	88	0.106	0.113	15.6	18.0	2.4
24	V. S.	21	95/65	83	0.108	0.120	15.0	16.7	1.7
25	P. H.	21	110/60	66	0.087	0.108	11.1	13.6	2.5

The position of the crest or summit is easily recognized in records of the radial and finger pad pulses from normal subjects, and also in many cases of hypertension and arteriosclerosis. However, when the summit of the pulse wave is flattened or modified by small secondary waves (e.g., the Zwischenschlag) or by ascent of the incisura, it may be very difficult to identify the true crest of the primary wave (Fig.

1*D-E*). Decision in such cases may be arbitrary. Fortunately, the number of such instances in the case of the finger pad pulses is very small, but they are a regular occurrence in the case of the volume pulses of the skin of the head.

Our values for the radial crest times (Table I) on normal subjects agree with those of Yamaguchi. The crest time for the volume pulse of the finger pad is slightly longer than that of the radial (Table I).

It is convenient to express the crest time in per cent of the duration of the total pulse cycle. When this is done, it is found that the radial crest time normally is between 10 and 16 per cent of the pulse cycle, and the digital crest time from 0 to 4 per cent longer; the most frequent difference between the two is from 1 to 3 per cent (Table I). In no case was the digital crest time shorter than the radial. It should be noted that these calculations are based upon average pulse wave duration during one complete respiratory cycle; the wave undergoes slight variations during respiration.

This relation between the duration of the primary waves (Hauptgipfel) of the radial and digital pulses is the reverse of that between the subclavian and cubital pulses. It is generally known that, in the more central arteries, the crest of the wave travels more rapidly than its base. As a result, the crest gains on the base, and the crest time shortens as the wave proceeds along the artery. Increased resistance, however, has an opposite effect, in that it slows the propagation of the crest of the wave.[19] It is possible, therefore, that the usual delay between the peaks of the radial and digital primary waves (''crest times'') is the result of a slightly elevated resistance peripheral to the radial artery.

In comparing normal radial and digital volume pulses, one notes that the incisura occurs uniformly higher on the catacrotic limb of the digital wave than on that of the radial. The height of the incisura varies during a respiratory cycle; it is higher on the catacrotic limb during expiration. There is a similar variation in the height of the incisura of the radial pulse during the respiratory cycle.

The incisura tends to be higher on the catacrotic limb as age increases, but this is not necessarily so. An attempt to find a relation between age and the relative height of the incisura met with failure. The tendency of the incisura to rise on the digital wave when constriction of the finger vessels occurs may be an important reason for our inability to obtain a correlation between its relative position and age. The tonus of the finger vessels is extremely labile; it varies as a result of thermoregulatory requirements, psychic influences, noises, etc. Constant conditions would be provided only by maximal dilatation, which is not readily obtained except by means of special techniques. It seems, however, that the height of the radial incisura is usually less than half that of the peak of the pulse, and that the digital incisura occurs at a variable height in excess of half that of the peak of the pulse.

Persons in the late thirties and forties may have the same wave form as younger subjects. Fig. 4 illustrates three such cases. The blood pressure in each case was below 120/80.

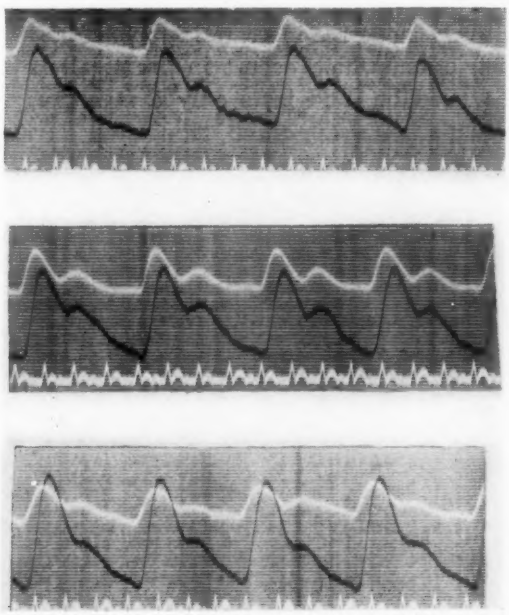

Fig. 4.—Normal finger pad and radial volume pulses. White record, radial; black record, finger pad. Time, 0.2 sec. Top figure from a man, 45 years old (G.B., Table I); middle figure from a man, 42 years old (A.H., Table I); lower figure from a man, 36 years old (R.M., Table I).

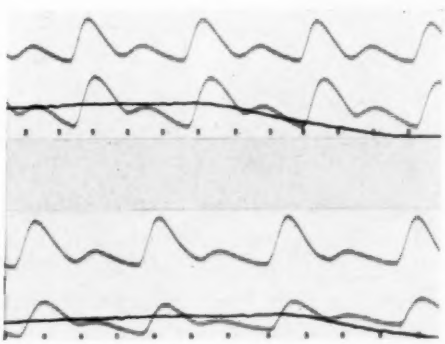

Fig. 5.—Effect of vasoconstriction in finger pad on the volume pulses of the radial artery (upper record in each figure) and of the finger pad (lower record in each figure). Figures are not continuous.

It was important, before trying to interpret records taken from obviously pathologic subjects, or from subjects who did not fit into our definition of normal, to try the effect of constrictor influences on the wave form in normal subjects. Fig. 5 illustrates the effect of immersing the opposite hand in water at 4° C. The constrictor effect is obvious, but there was no alteration in "crest time" nor in the fundamental form

of the wave. The effects of "psychic" constriction are similar to those produced by cold. It may be argued that such stimuli do not produce an adequate response, but we were not interested in the effects of complete obliteration of the lumina of the finger vessels, but only in the effects of a relatively moderate increase in tone. Many observations on "psychic" constriction, which occurs in practically every case when the camera is turned on, and lasts only a few moments, show that it produces no fundamental alteration of the form of the volume pulse in the radial and digital arteries of normal subjects.

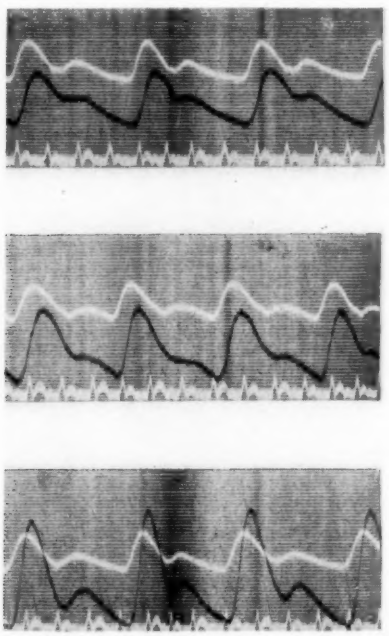

Fig. 6.—Effect of amyl nitrite on the volume pulses of the radial artery (white record) and of the finger pad (black record). Top figure before, middle figure during, and lower figure three minutes after administration of the drug. Time, 0.2 sec.

That moderate changes in the tone of the finger vessels do not influence the crest times of the finger pad volume pulses is further supported by the effects of amyl nitrite inhalation (Fig. 6). The increase in the dicrotism of both the digital and radial waves is evident. Similar effects were reported by Matthes, Gross, and Gopfert,[5] and by Mann.[20] Differences in the amplitude of the finger volume pulses in this record are arbitrary, for it was necessary to increase the amplification because of the constriction induced by administration of the drug, yet there is no significant difference in the fundamental form of the waves (excepting the dicrotism) or in the crest times in any of the records. It must be admitted that the circulatory action of this drug is extremely complex. The development of dicrotism in the finger pad pulses at the time when the finger vessels were constricting as a result of the sympathetic excitement induced by the drug poses an interesting problem.

A study of the crest times in relation to variations in resting heart rates (Table I) showed nothing important.

B. Arterial Disease:

Yamaguchi[18] found that the crest time (time to the peak of the primary wave) was absolutely and also relatively proportional to the duration of the pulse cycle in certain types of vascular disease, such as nephrosclerosis, chronic nephritis, arteriosclerosis, and hypertension. That is by no means a new concept, but it had never been quantitated. We were interested in confirming his observations, in extending them to the digital pulse wave, and in studying any differentiating characteristics.

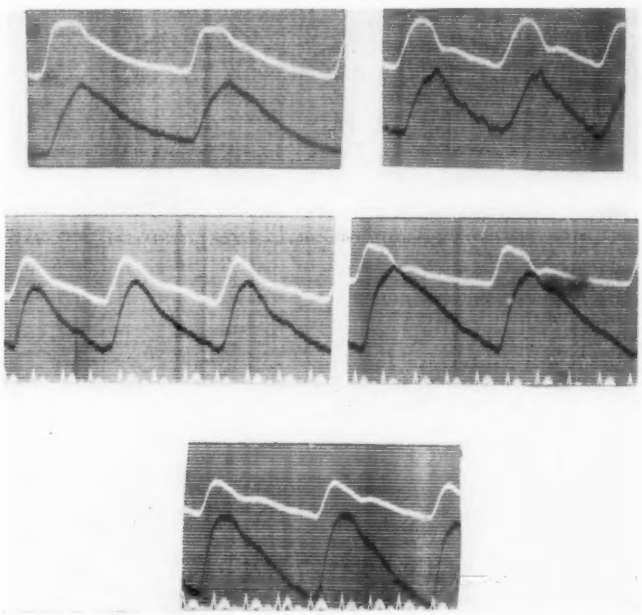

Fig. 7.—Volume pulses in arteriosclerosis without hypertension. Radial, white. Finger pad, black. Time, 0.2 sec. Top left figure: man, 78 years old (C.B., Table II). Top right figure: man, 75 years old (D.S., Table II). Middle left figure: woman, 34 years old, B.P. 120/80, severe nephritis several years previously; at the time records were made the urine was normal and there was no evidence of sclerosis in retina; radial crest time, 0.125 sec.; digital crest time, 0.16 sec. Middle right record: (J.P., Table II) no clinical evidence of arteriosclerosis. Lowest figure: medical student (W.M., Table II), hyper-reactor to cold-pressor test.

1. *Sclerosis.*—Records of the radial and digital volume pulses of two old men are shown in Fig. 7. The crest times in these cases were markedly increased. Both men had advanced arteriosclerosis (marked palpable sclerosis and tortuosity of main arteries; retinal arteries only slightly tortuous, with no broadening of light reflecting band). Their blood pressures were consistently below 120/80.

As the number of subjects studied increased, it became apparent that, in certain younger persons, changes occurred in the contour of the digital waves which were not apparent in radial tracings alone. These

younger subjects had normal blood pressures and showed no gross evidence of arteriosclerosis (either by arterial palpation or ophthalmologic examination), yet the digital wave form was fundamentally abnormal and resembled that of the older subjects (Fig. 7; note the increase in the digital crest times). For this reason we have placed these subjects

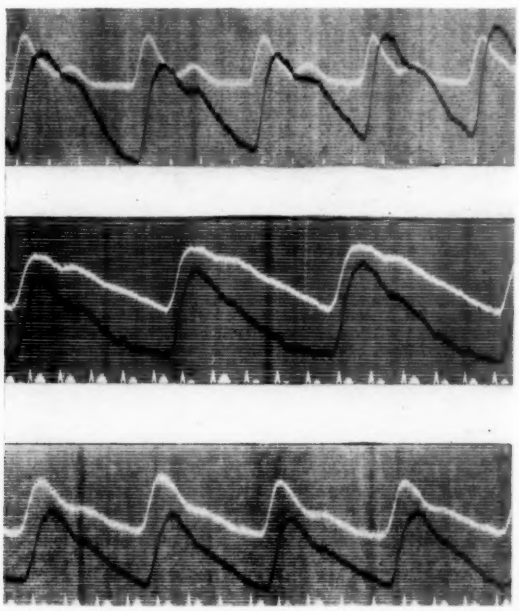

Fig. 8.—Volume pulses in subjects without clinical evidence of arteriosclerosis and with normal blood pressures. Radial, white; finger, black; time = 0.2 sec. Top figure: J.H., Table II. Middle figure: man, 47 years old, B.P. 112/75; radial crest time, 0.14 sec.; digital crest time, 0.21 sec. Lower figure: F.K., Table II.

TABLE II

RADIAL AND DIGITAL CREST TIMES IN SUBJECTS WITH ARTERIOSCLEROSIS

NO.	SUBJECT	AGE (YRS.)	RESTING BLOOD PRESSURE	PULSE RATE	RADIAL CREST TIME IN SEC.	DIGITAL CREST TIME IN SEC.	RADIAL CREST TIME AS % OF PULSE CYCLE	DIGITAL CREST TIME AS % OF PULSE CYCLE	DIFFERENCE BETWEEN RADIAL AND DIGITAL CREST TIMES IN % OF PULSE CYCLE
1	R. P.	22	110/64	95	0.100	0.125	13.9	19.6	5.7
2	N. M.	23	110/70	64	0.100	0.150	10.6	16.0	5.4
3	C. B.	78	120/70	84	0.175	0.205	24.6	28.8	4.2
4	F. M.	44	120/80	66	0.140	0.205	14.8	22.2	7.4
5	R. H.	25	88/54	77	0.087	0.133	11.7	17.7	6.0
6	W. M.	22	112/72	81	0.113	0.175	15.2	23.7	8.5
7	D. S.	75	118/75	72	0.118	0.213	14.2	25.6	11.4
8	J. P.	40	100/60	62	0.100	0.220	10.3	22.3	12.0
9	J. H.	40	110/70	90	0.094	0.150	14.2	22.6	8.4
10	F. K.	50	120/80	77	0.140	0.190	17.9	24.6	6.7

in the arteriosclerotic group, although the absence of other positive evidence should be emphasized. This does not mean that a more comprehensive examination of the arterial system (arteriography, etc.) would not have revealed arteriosclerosis.

Fig. 8 illustrates records from subjects who did not show arteriosclerosis on clinical observation (arterial palpation, ophthalmologic examination). A comparison of these records with those of obviously arteriosclerotic subjects (top figures of Fig. 7) suggests either that the process of sclerosis is under way in the smaller vessels, or that changes in the elasticity of these vessels or of the tissues have proceeded far enough to alter the propagation of the pulse wave in the finger arteries.

One feature is common to all these subjects, namely, an increase in the crest time of the digital volume pulse. In all except the top record of Fig. 8, the incisura and the rebound wave which follows it have disappeared from the finger pulses. The contour of the radial volume pulse shows considerable variation. In the top record of Fig. 8 and the bottom record of Fig. 7 the radial pulses are normal in appearance; the remainder of the radial pulses show changes in contour which have been generally ascribed to arteriosclerosis. These changes may also occur in subjects who have no clinically recognizable arteriosclerosis.

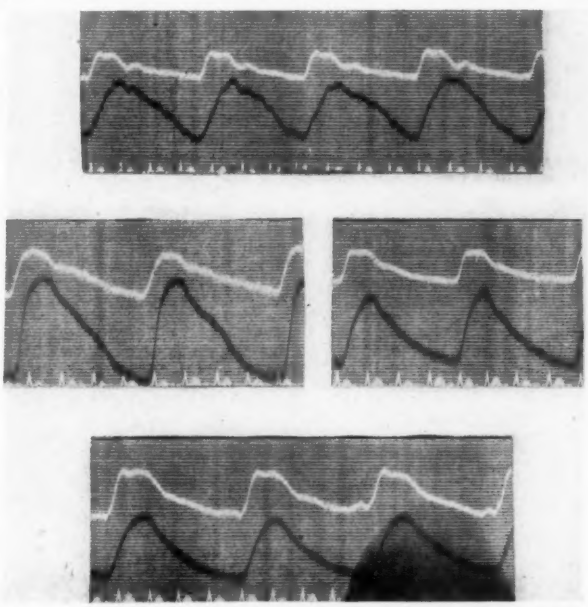

Fig. 9.—Volume pulses in subjects with hypertension. Radial, white; finger pad, black. Time, 0.2 sec. Top figure: L.C., Table III. Middle left figure: A.M., Table III. Middle right figure: H.S., Table III. Lowest figure: N.S., Table III.

2. *Hypertension.*—Records taken from patients with hypertension are illustrated in Fig. 9. The similarity between the records from patients with hypertension (Table III, Figs. 9 and 10) and those from patients with arteriosclerosis, but without hypertension, is obvious (Table II,

Figs. 7 and 8). An increase in crest time, loss of the rebound wave in both the digital and radial pulses, triangulation of the digital pulse, and rounding and flattening of the radial pulse are common to both groups. All records from patients with fairly long-standing hypertension presented similar features.

An interesting case of malignant hypertension is presented in Fig. 10 (A.B., Table III). The patient complained of headaches, dizziness, weakness, and dyspnea. Ophthalmologic examination revealed very tortuous arteries which branched at right angles and had broad light reflexes. Some of the arterial branches were markedly constricted. The nonprotein nitrogen content of the blood was 45 mg. per cent. She had had a bilateral lumbar sympathectomy and splanchnicotomy three years before we made our observations. The abnormalities in the contour of

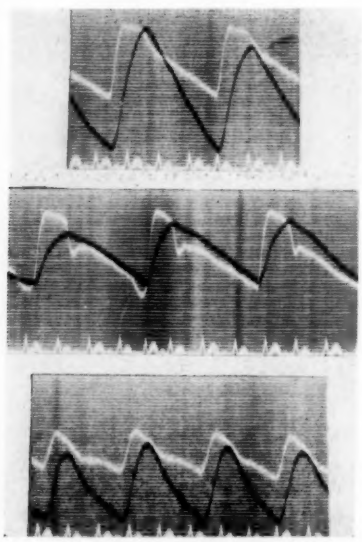

Fig. 10.—Volume pulses in a case of malignant hypertension (A.B., Table III). Radial, white; finger pad, black. Time, 0.2 sec. Top figure, "resting" record. Middle figure, during "psychic" vasoconstriction. Lowest figure, after amyl nitrite.

her radial and digital volume pulses are obvious in the top record. In the middle record one sees the effect on the form of the pulse of a constriction of psychic origin. The most significant thing was the appearance in the radial record of a notch and wave which were grossly similar in position to the normal rebound wave; they disappeared when the digital vessels relaxed. It is interesting to note that there was no change in the crest time. This record suggests that reflection of waves from the periphery may contribute to the formation of the radial wave. The bottom record shows the effect of amyl nitrite on the contour of the waves. There was no fundamental alteration. The crest times were shortened absolutely, but not relatively in proportion to the duration of the pulse cycle.

TABLE III

RADIAL AND DIGITAL CREST TIMES IN SUBJECTS WITH HYPERTENSION

NO.	SUBJECT	AGE (YRS.)	RESTING BLOOD PRESSURE	PULSE RATE	RADIAL CREST TIME IN SEC.	DIGITAL CREST TIME IN SEC.	RADIAL CREST TIME AS % OF PULSE CYCLE	DIGITAL CREST TIME AS % OF PULSE CYCLE	DIFFERENCE BETWEEN RADIAL AND DIGITAL CREST TIMES IN % OF PULSE CYCLE
1	P. S.	40	180/110	80	0.075	0.125	10.7	16.7	6.0
2	S. S.	40	190/110	77	0.163	0.237	21.0	30.6	9.6
3	A. B.	27	185/110	92	0.217	0.242	27.6	30.4	2.8
4	L. K.	34	130/80	76	0.125	0.160	19.2	24.6	5.4
5	L. M.	24	140/110	88	0.087	0.113	12.9	18.2	4.3
6	J. S.	23	125/70	77	0.087	0.119	11.1	15.1	4.0
7	B. D.	47	235/135	100	0.125	0.147	20.0	24.0	4.0
8	N. S.	53	200/100	67	0.117	0.225	13.1	25.0	11.9
9	J. G.	23	140/86	77	0.123	0.188	15.8	24.2	8.4
10	J. W.	50	188/112	96	0.130	0.149	20.4	23.6	3.2
11	L. C.	40	210/120	77	0.085	0.225	11.0	28.8	18.8
12	A. M.	54	200/110	80	0.113	0.187	13.6	22.7	9.1
13	H. S.	60	170/110	77	0.087	0.188	11.2	24.0	13.8
14	N. S.	53	200/120	67	0.118	0.225	13.1	25.0	11.9

Yamaguchi[18] and Matoba[7] showed that an increase in radial crest time in arterial disease is not caused by bending or breaking of the primary wave, but by accentuation of a small wave between the peak of the primary wave and the incisura which they call Zache II. Greven and Federschmidt[4] and Matthes, et al.,[5] showed that this wave was the cause of the increase in crest time in both the radial and digital pulses. They call this wave the Zwischenschlag. This wave may or may not be visible in the sphygmograms of normal persons. When it is present, it is very small (Fig. 2, third row left, radial; Fig. 4, top, radial). These authors are of the opinion that increased peripheral resistance is responsible for the augmentation of this wave. Judging from various records which are not shown, one finds it probable that the augmentation of the Zwischenschlag is responsible for the increase in radial and digital crest times. The relation of this wave to the increase in crest time is clearest in young subjects, or when the alteration in vascular dynamics is not of long standing. Presumably, the factor of organic change in the vessel walls determines whether the wave can be recognized.

The vibrations on the anacrotic and catacrotic limbs of the digital pulses in the upper right record of Fig. 7 and the upper record of Fig. 9 may have originated in the vessel wall and have been caused, in part, by resistance. They are not instrumental in origin. They usually occur regularly in persons who show them. They diminish with a decrease, and increase with a rise, in the tone of the vessels; the change in tone is indicated by the amplitude of the volume pulse. The vibra-

tions may increase on the digital wave, with restoration of the radial contour to its fundamental form. They do not possess a regular frequency, but may be compared to audible "noise." They are usually absent in young, normal subjects, but they have appeared in several cases of hyper-reactors to cold who had increased tonus of the digital vessels; they disappeared, during rest in bed, from the digital pulse of a young girl with hypertension, and reappeared when she resumed her occupation. It is possible that some of these vibrations may have their origin in fine tremors. Their significance is not clear.

DISCUSSION

The pulse wave data presented in this paper suggest that the *effects of arteriosclerosis and hypertension on the dynamics of the arterial system appear in the vessels of the finger pad before they do in the radial artery.* In our series of records showing alterations in the contour of the radial pulse there have always been changes in the digital pulse, as well, but these were not always accompanied by alterations in the simultaneously recorded radial pulse (Fig. 7, bottom record; Fig. 8, top and bottom records). Further evidence in support of this statement is found in the fact that changes in the radial pulse may be less marked than those in the simultaneously recorded digital pulse (Figs. 7, 8, and 9). These observations suggest that the contour of the digital pulse is a better indication of the condition of the peripheral arteries than is the contour of the radial pulse. It is apparently impossible to predict with accuracy the contour of the digital pulse from the contour of the radial pulse in subjects with altered arterial dynamics.

Interpretation of the origin of the alterations in digital pulse contour in arteriosclerosis requires a detailed correlation between the pulse contour and other objective signs, such as radiographic data and vasodilator tests. This has not yet been attempted. However, there was neither palpable sclerosis of the main arteries nor sclerosis of the retinal arteries in our younger subjects (Fig. 7, middle and bottom rows; Fig. 8), but these subjects showed the same changes in the digital pulse that occurred in subjects with recognizable sclerosis (Fig. 7, top row).

The rebound wave (following the incisura) in the digital pulse tends to disappear in subjects with increased arterial pressure (Figs. 9 and 10). This has also been observed by Matoba[7] and Greven and Federschmidt.[4] The exact cause of the loss of the rebound wave is not known. It may be that, in young persons with hypertension, the rebound wave is damped by interference with other reflected waves. In patients with more severe and long-standing hypertension, it is possible that the smoothing of the digital wave, with loss of all evidence of secondary waves, is caused by organic changes in the vessel wall (Figs. 9 and 10). Tending to confirm this opinion is the type of digital wave which occurs in subjects with sclerosis but without hypertension (Fig. 7).

It is possible that the differences between the normal radial and digital pulse waves are caused by a slight increase in peripheral resistance as the pulse wave passes from the radial artery. It is difficult, if not impossible, to attribute the differences between these two waves in subjects with arteriosclerosis and with hypertension to increased peripheral resistance alone, for moderate, and even marked, increases in the tone of the finger vessels fail to produce these differences in normal subjects.

We are uncertain as to the location of this resistance. It may be in the digital arteries or in the small arteries and arterioles of the finger pad. Additional observations bearing on this question are: (1) the diastolic pressure in the vessels of the volar arch usually exceeds that in the radial artery;[2] (2) the pulse wave velocity diminishes between the radial artery and the digital vessels;[4, 5] (3) constriction of the finger vessels produced by vasomotor reflexes (see above) does not alter the digital crest times in normal subjects. These facts might be considered as indicating that the resistance which is responsible for the slight prolongation of digital crest time is located in the digital arteries. The extent of their participation in moderate vasoconstrictor reflexes has not been ascertained. If experience in comparing radial artery and finger pad artery reactions[13] can be used as a guide, the digital arteries did not constrict while the vasomotor reflexes were acting. In the absence of direct evidence, this is consistent with the fact that the digital crest time was not affected by constriction in the pad.

A reasonable interpretation of the data in this paper is possible along the following lines: The fact that the arteries act as an elastic reservoir is well known. Greven and Federschmidt[4] have suggested that there may be two reservoirs, a central and a peripheral. The peripheral elastic reservoir is postulated as beginning somewhere peripheral to the radial artery. They suggested this because of their observation that the pulse wave velocity in the radial-digital span is less than it is in the brachio-radial span. They are of the opinion that this would not be so if the entire arterial system acted as one elastic reservoir. Matthes, Gross, and Gopfert[5] made similar observations and are of the same opinion as Greven and Federschmidt. They make the further suggestion that this peripheral elastic reservoir has lower elastic limits than the central one. Neither group was able to define the anatomic limits of this theoretical reservoir. The alterations in wave form which occurred in our subjects with hypertension (Figs. 9 and 10) and with arteriosclerosis (Figs. 7 and 8), and the discrepancies between the radial and digital pulse contours in the younger subjects with these abnormalities (Fig. 7, bottom) further support the idea that there is such a system.

If the existence of a peripheral elastic reservoir be admitted, the normal and pathologic digital pulse contours may be explained as follows:

1. *In normal subjects the pulse wave meets with slight resistance upon entering the arteries peripheral to the radial, namely, the volar arch, digital arteries, and finger pad arteries.* This is indicated by the slight increase in crest time of the digital pulse (Table I). In normal persons the capacity of the elastic reservoirs made up by these arteries is sufficiently great that moderate constriction (the exact arterial participation cannot be defined, Fig. 5) does not cause alterations in the fundamental pulse contour or crest times. For this reason one does not obtain evidence for the presence or absence of such an elastic system from the pulse contours of normal subjects. (Matthes, et al.,[5] show several records of digital pulses which they say were obtained from normal subjects. From our data we would classify them as abnormal. They use these records as evidence that there is a peripheral elastic reservoir, but give no information as to what they consider normal records.

2. Accepting the possibility that the peripheral reservoir is less elastic than the central, it is *also possible that alterations affecting the properties of the vessel walls,* such as arteriosclerosis or hypertension, *would first become apparent in the peripheral reservoir.* This would explain two observations: first, that the digital wave form may be altered to a greater degree than the radial wave form; and, second, that alterations in the digital wave form are not necessarily accompanied by alterations in the radial wave form. It would seem that the latter phenomenon is accounted for by greater elasticity of the radial artery, for more perfect reflection of waves of peripheral origin would be expected in cases of hypertension and arteriosclerosis if the elastic properties of the vessels were the same. It seems probable that alterations in the radial pulse contour occur either when reflection from the periphery is sufficiently great to overcome this difference in elasticity, or when the elastic properties of the radial artery have been reduced by sclerosis.

Although the data in this study constitute indirect and inconclusive evidence, they suggest the possibility that changes in the finger pad pulses may be a very early indication of loss of elasticity of the arteries contributing to the propagation and modification of the pulse in the pad. The role played by the larger arteries of the hand (volar arch, digital arteries) and the small arteries and arterioles of the finger pad with respect to the form of the volume pulse in the pad has not been ascertained. This point is of importance to the objective of this study, for it had been hoped that recording the pulse wave in the minute arteries would help in the diagnostic evaluation of their condition. The data which have been obtained promise to aid in this attempt.

SUMMARY AND CONCLUSIONS

1. The volume pulses in the finger pad and radial artery were studied by means of previously described photoelectric plethysmographs.

2. The normal digital pulse has essentially the same contour as the normal radial pulse.

3. In normal subjects, the interval between the base and the peak of the digital pulse wave, which we have termed the "crest time," is slightly greater than that of the radial pulse wave. The fact that the crest time of the digital pulse wave is longer than that of the radial suggests that the pulse encounters slightly increased resistance in the vessels of the hand and finger.

4. In arteriosclerosis and hypertension, the contour of the digital pulse is altered earlier and to a greater extent than that of the radial pulse. This change in contour results in an increase in crest time, accompanied by obliteration of the incisura and rebound wave. In young persons with hypertension, and in some subjects with hypertensive tendencies, irregular vibrations are present on the catacrotic limb of the digital pulse. They are less common on the radial pulse. The changes which occur in the contour of the digital pulse are always greater than those in the radial.

5. In hypertension and arteriosclerosis it is not possible, because of discrepancies in the alterations which take place in the waves, to predict from the radial pulse contour what the digital pulse contour will be.

6. Study of the form of the digital pulse does not enable one to differentiate arteriosclerotic changes in the finger vessel wall from those produced by hypertension, if the hypertension is of long standing.

7. The differences between the digital and radial pulse contours are probably caused by a difference in the elastic properties of the vessels, as has been suggested by others. This difference is not apparent in the pulses of normal subjects, but becomes evident in cases of arteriosclerosis and hypertension in which the normal arterial dynamics are altered.

8. The suggestion is made that the form of the finger pad pulse may contribute information on early changes in the elasticity of the arterial system which influence this pulse.

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SPONTANEOUS VOLUME CHANGES IN THE EXTREMITIES

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VARIATIONS in hand volume, apparently spontaneous in nature, have been described by various authors.[1-3] The significance of these changes, however, has not been adequately analyzed. Since some doubt has recently been cast upon the view that changes in the volume of an organ are directly related to alterations in blood flow,[4, 5] it was thought worth while to investigate the spontaneous variations in limb volume, in the hope that more information might be gained as to the mechanism involved.

METHOD

Eighty-one experiments were performed on forty-seven normal subjects whose ages ranged from 12 to 74 years. The plethysmographic method was used, with the technique previously described.[1, 6] The room temperature varied between 25 and 27° C., and the temperature of the water in the plethysmograph (bath temperature) was generally 32° C. In some instances, readings were obtained at bath temperatures of 19° and 45° C. In most experiments a contralateral hand and forearm, or hand and leg, were investigated simultaneously. The foot was studied in a number of cases. Special precautions were taken to eliminate external stimuli, and the subject was encouraged to relax mentally and physically. In some instances, the experiments were performed during sleep.

A base line was obtained by raising the Brodie's bellows to a mid-position, and limb volume changes were recorded on a slowly moving drum. The variations were calculated in cubic centimeters of increase or decrease per 100 c.c. of limb volume, using the base line, when it was temporarily maintained at a steady level, as a point of reference. For the purpose of tabulation, the results were divided into four groups: (1) marked variations (more than 0.6 c.c. per 100 c.c. of limb volume), (2) moderate variations (varying from 0.2 to 0.6 c.c.), (3) slight variations (less than 0.2 c.c.), and (4) no changes (constant base line). In a number of experiments the rate of blood flow was also measured.

In the case of the forearm and the leg, volume changes and blood flow readings were recorded with a pressure of 250 to 300 mm. Hg applied to the wrist and the ankle respectively, in order to eliminate all influences of vascular changes in the hand and foot.[7] In a few instances, base lines were obtained without this pressure. In the case of the hand, the effect of an elevation of venous pressure upon the spontaneous volume changes was investigated on numerous occasions. This was accomplished by maintaining a pressure of 70 to 80 mm. Hg either at the arm or forearm until the pressure in the veins of the hand had reached approximately the same level, and then recording a base line under these conditions.

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RESULTS

1. Volume Changes in the Hand.

A. *Bath Temperature of 32° C.*—The hand was studied in forty-three subjects, and in a number of these the experiments were repeated from one to nine times. Spontaneous variations in limb volume were portrayed by sudden rises and falls of the base line, which varied in amplitude and occurred in an inconsistent and unpredictable fashion (Figs. 1 and 2*B*). A relatively constant level was maintained for only short periods at the crests and troughs of the waves. Simultaneous base line observations on the two hands revealed that the variations in

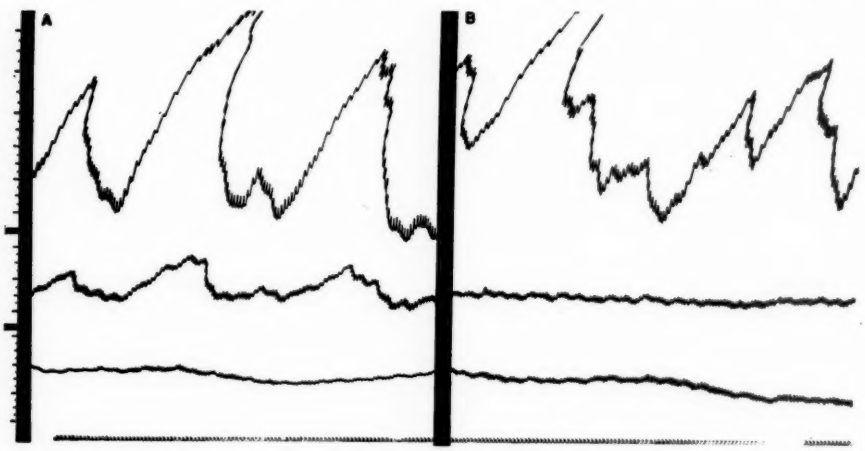

Fig. 1.—Spontaneous volume changes at a bath temperature of 32° C. and room temperature of 25° C. Subject, L.K. *A*. Upper curve shows spontaneous variations in hand volume; middle curve, spontaneous variations in forearm volume which occurred without applying pressure at the wrist; bottom curve, constant leg volume with no pressure applied at the ankle. *B*. Upper curve, hand volume, same as in *A*; middle curve, constant forearm volume with a pressure of 300 mm. Hg at the wrist; bottom curve, constant leg volume with a pressure of 300 mm. Hg at the ankle. Time in seconds. Calibrations in 0.25 c.c.

volume were synchronous in the two extremities. Since the degree of spontaneous volume changes was found to be fairly constant from time to time in any one subject, it was possible to classify the results of the different experiments as follows: marked variations, twelve subjects; moderate variations, eleven subjects; slight variations, four subjects; and no variations, sixteen subjects. Of the twelve subjects with marked variations, eleven were in the second and third decades and one in the early part of the fourth decade. Seven of the eleven subjects who had moderate variations were between 19 and 35 years of age, and the remaining four were beyond the fourth decade. Of the four with slight variations, two were less than 35 years of age and two were elderly persons. Eleven of the sixteen subjects with no spontaneous variations were in the fourth to the eighth decades, and the remaining five were under thirty years of age.

B. *High and Low Bath Temperatures.*—In sixteen experiments the hand was exposed to a bath temperature of 45° C. Whereas in every instance the base line had previously exhibited marked or moderate variations at 32° C., it was now maintained at a constant level (Fig. 2*C*), except in one instance. At a bath temperature of 19° C. there were no variations, or, at most, only slight changes (Fig. 2*A*).

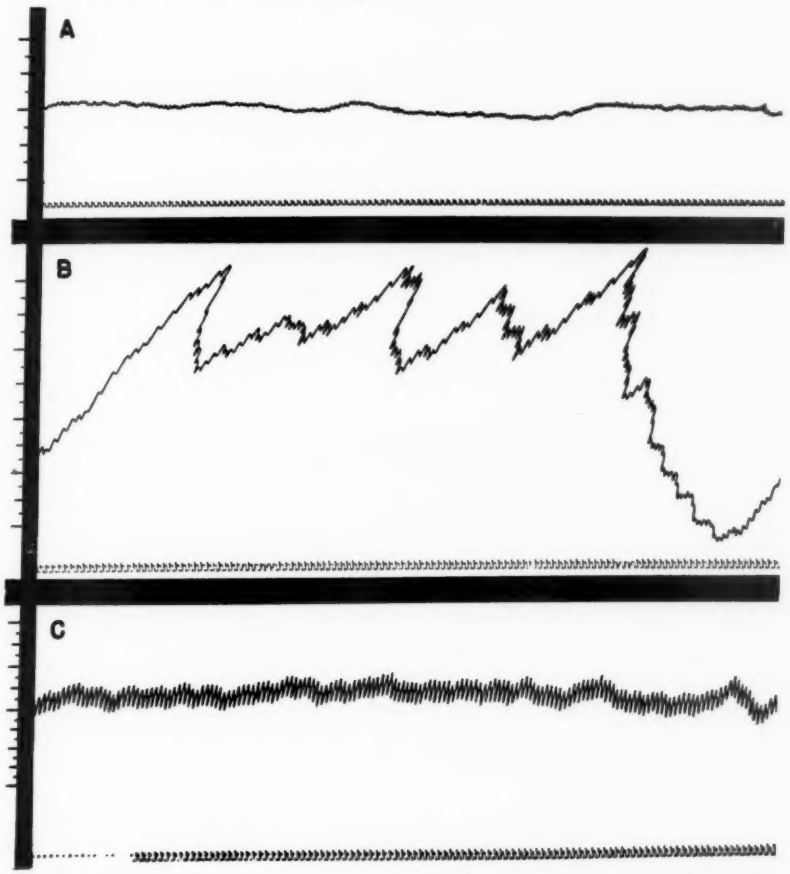

Fig. 2.—Effect of various bath temperatures upon magnitude of variations in hand of subject, D.A. *A*, 19° C.; *B*, 32° C.; *C*, 45° C. Room temperature, 26° C. Calibrations in 0.25 c.c. Time in seconds.

C. *Effect of Sleep at Bath Temperature of 32° C.*—Hand volume changes during sleep were studied in five subjects who showed a constant base line while awake. The response in the case of one young normal adult was typical, and is of particular interest because he was one of the few in his age group whose base line was steady. However, when he fell asleep during the course of the experiment, spontaneous variations in the volume of the hand appeared, and differed in no way from those which occurred in other young subjects (Fig. 3*B*). In the remaining four subjects, who were in the fourth to the sixth decades,

variations in hand volume were also observed during sleep, but the response was not as marked as in the case of the young adult. When the subjects awoke, the magnitude of the spontaneous volume changes usually decreased, but, as a rule, the base line remained somewhat less constant than before sleep occurred.

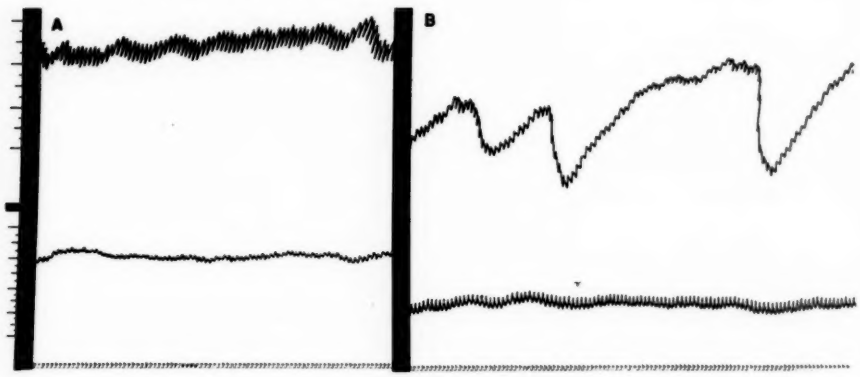

Fig. 3.—Effect of sleep upon spontaneous volume changes in hand of subject, L.W. *A*, Subject awake. Upper curve, constant hand volume; lower curve, constant forearm volume. *B*, Subject asleep. Upper curve, spontaneous variation in hand volume now present; no change in volume of forearm. Bath temperature, 32° C. Room temperature, 26° C. Calibrations in 0.25 c.c. Time in seconds.

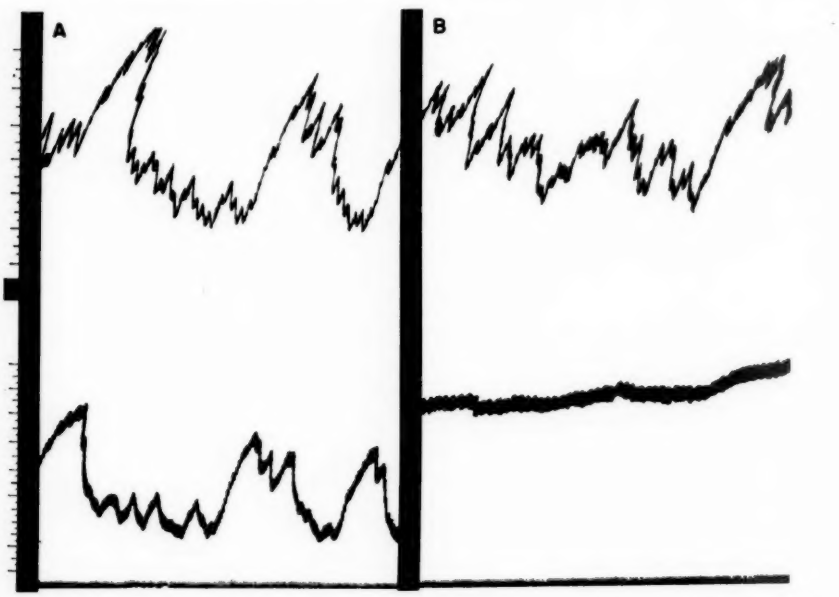

Fig. 4.—Volume changes recorded simultaneously in both hands of subject, K.K. *A*, Upper curve, right hand; lower curve, left hand. Synchronous variations present. *B*, Pressure of 70 mm. Hg at wrist of left hand. Upper curve, variations in right hand volume unchanged; lower curve, no variations in volume now observed in left hand. Bath temperature, 32° C. Room temperature, 26° C. Calibrations in 0.25 c.c. Time in seconds.

D. *The Effect of Raising Venous Pressure in the Hand.*—In eighteen subjects with marked or moderate variations in the volume of the hand,

raising the local venous pressure to 60 or 70 mm. Hg usually resulted in complete abolition of the spontaneous volume changes (Fig. 4*B*). In only a few cases did slight variations persist, but the changes in no way compared to those recorded previously. Simultaneous observations on the control hand showed that the spontaneous variations continued to occur (Fig. 4*B*).

2. Volume Changes in Other Parts of the Extremities.

The forearm, at a bath temperature of 32° C., was studied in thirty-nine subjects; thirty-four maintained a constant base line (Figs. 1*B* and 3*A*), and four showed slight, and one, moderate, variations. In those instances in which the arterial occlusion pressure at the wrist was removed, allowing the venous return from the hand to enter the forearm, variations synchronous with those observed in the hand, but of a lesser magnitude, usually became evident (Fig. 1*A*). The leg volume was found to be constant in eight of eleven subjects (Fig. 1*B*), while slight variations were observed in the remaining three. Only minor volume changes occurred in the feet of the four subjects who were examined.

DISCUSSION

When the data presented are considered, it would seem that spontaneous limb volume changes are limited almost exclusively to the hand. The fact that some subjects who ordinarily showed no volume changes exhibited marked variations when they were asleep would be in favor of the view that these volume changes are truly spontaneous, and not the result of mental activity or of the action of sensory stimuli upon the tonus of blood vessels. This is further supported by the fact that the variations were abolished by a bath temperature of 45° C., under which conditions the blood vessels in the hand still respond to external stimuli.[5]

Since transient volume changes in an organ are essentially vascular in nature, the question arises as to what types of vessels are responsible for this phenomenon. With the exception of Burton,[2] who points out that there is possibly a venous component in the production of the spontaneous variations, the consensus seems to be that volume changes in an organ or an extremity are caused by alterations in arterial inflow. It is obvious, however, that these variations may also result from transient changes in the quantity of blood in the veins. That the venous bed* can constrict independently of the arteries has recently been reported by Abramson and Ferris,[5] who found that both the hand and forearm respond to such stimuli as a pinch or mental arithmetic with a temporary diminution in limb volume. These changes were associated with a significant arterial constriction in the hand, whereas, in the forearm, either

*"Venous bed" includes those vessels which cannot constrict against an internal pressure of 70 to 80 mm. Hg and do not materially contribute to the peripheral resistance. They include veins, venules, and capillaries.

no change was produced or an arterial dilatation occurred. From these data it was concluded that the volume changes in the hand, incident to a pinch or mental arithmetic, are the result of alterations in tone of both the arteriolar and venous beds, whereas, in the forearm, the response is almost entirely venous in nature. This view was supported by the observation that changes in forearm volume could no longer be elicited if the local venous pressure were first raised to 70 to 80 mm. Hg, under which conditions, according to Lewis,[8] the venules and capillaries in the skin are prevented from constricting. Therefore, our observation that spontaneous variations in the hand are eliminated by a similar procedure would be in favor of the assumption that these volume changes likewise result from alterations in venous tonus.

The objection might be raised that arterial inflow to the hand is materially interfered with by the presence of an artificially raised venous pressure. In order to test this possibility, we proceeded to ascertain the effect of the external application of different pressures at the wrist on blood flow to the hand. Since the usual procedure for the measurement of blood flow is inapplicable when venous pressure is high, it was necessary to resort to the following indirect means. Blood flow figures were first obtained on the forearm with no arterial occlusion pressure at the wrist, under which conditions the readings were the resultant of arterial inflow to the forearm and venous return from the hand, and the latter was directly proportional to the arterial inflow to the hand. Then, different pressures were applied and maintained at the wrist until the venous pressure in the hand reached a similar level and the outflow became equal to the inflow. By making blood flow measurements on the forearm under these conditions, information could be obtained as to whether or not there was any change in venous return from the hand, and, hence, in arterial inflow. Using this method, it was found that, in subjects with a normal or slightly elevated systemic blood pressure, external pressures varying from 40 to 60 mm. of Hg, which ordinarily reduce or completely abolish spontaneous variations, did not alter venous return from the hand, whereas a pressure of 70 mm. decreased it, but not significantly.

Occasionally, when both hands were utilized in order to study volume changes in one and blood flow in the other, it was noticed that spontaneous increases and decreases in arterial inflow were accompanied by rises and falls in the base line. This might suggest a causal relationship between the two phenomena. However, the observation that in other subjects variations in arterial blood flow were not accompanied by volume changes (Fig. 5) would tend to support the view that spontaneous changes in arterial inflow, of the magnitude generally observed in the hand, do not materially affect its volume. This is in accord with the observations of Holt and Lawson,[4] who found that

there could be significant changes in blood flow through the dog's hind leg with only slight variations in limb volume. These facts, however, do not rule out the possibility that a *significant* reduction in arterial inflow will decrease hand volume. For example, as has been stated before, Abramson and Ferris[5] found that with a strong, noxious stimulus, such as a pinch, a marked decrease in flow to the hand results, and, under these conditions, a diminution in hand volume may occur, even when the venous effect is eliminated by the application of a pressure of 70 to 80 mm. Hg to the wrist. Therefore, in the presence of marked spontaneous alterations in arterial inflow, an arterial factor may play a part in producing the changes in hand volume.

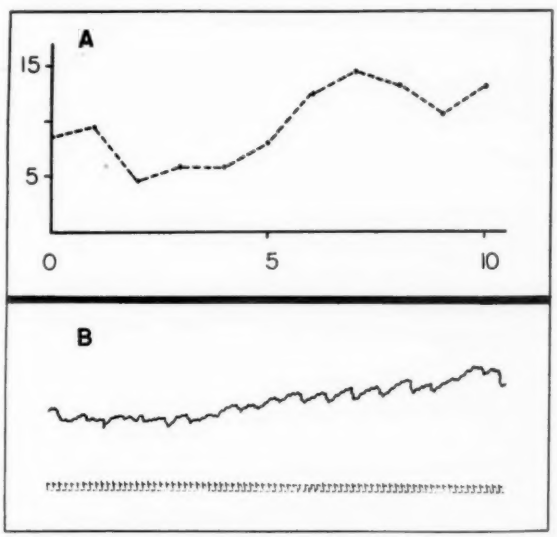

Fig. 5.—Blood flow measurements and volume changes in the hand of the same subject, L.A. *A*, Graph depicting spontaneous variations in blood flow, representative of changes present throughout experiment. Abscissa, minutes. Ordinate, blood flow in cubic centimeters per minute per 100 c.c. limb volume. *B*, Curve representative of volume changes present throughout experiment. Time in seconds. Bath temperature, 32° C. Room temperature, 26° C.

Capps[10] has shown that the veins of the hand possess tonus which is subject to temperature changes, i.e., cold constricts them and heat dilates them. In this connection it is of interest that, in the case of the hand, the base lines were of different types at bath temperatures of 19°, 32°, and 45° C. Fig. 2 reveals the transition from a constant volume at the low temperature to marked spontaneous variations at 32°, and the return to a steady base line at the high temperature. This would tend to indicate that, when veins are excessively constricted or dilated by external factors, no spontaneous alterations in caliber occur, and that the maximal variability in size is present when the skin temperature is normal.

From the foregoing, it would seem that, under physiologic conditions, the hand is intermittently changing in volume largely as a

result of alterations in the quantity of blood present in the veins, venules, and capillaries, and that the capacity of this venous bed is, in turn, dependent upon changes in venous tone.

SUMMARY AND CONCLUSIONS

1. By means of the plethysmographic method, spontaneous variations of limb volume were studied in forty-seven normal subjects, including persons of all ages between the second and eighth decades.

2. Spontaneous variations were found to be characteristic of the hand, and were absent or insignificant in the forearm, leg, and foot.

3. These variations occurred most frequently in young, normal adults and less often in persons of advanced age. They were marked during sleep and disappeared at high and low bath temperatures.

4. Raising the venous pressure to 60 or 70 mm. Hg, which prevents venous constriction without materially affecting arterial inflow, consistently caused the variations in the hand to disappear.

5. It is concluded that spontaneous variations in the volume of the hand are largely the result of alterations in the caliber of the venous bed, although an arterial component probably also plays a role.

6. The studies presented lend further support to the view that changes in the volume of an extremity do not necessarily reflect alterations in arterial inflow.

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THE EFFECTS OF NITRITES AND XANTHINES ON CORONARY INFLOW AND BLOOD PRESSURE IN ANESTHETIZED DOGS

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DRUGS may be effective in improving myocardial blood supply by decreasing resistance to flow through normal channels or by dilating collaterals. The latter has been dealt with by several investigators.[1-4] This paper is concerned only with the former.

The empirical use of the nitrites began with the clinical observations of Brunton,[5] and, of the xanthines, with those of Babcock[6] and Askanazy.[7] The clinical trials were followed by many experimental investigations on the effect of these drugs on the heart and the coronary vessels. Such studies include observations on the inflow into the aorta or the coronary vessels, perfused under constant pressure,[8-11, 49] or on the outflow from the coronary sinus and/or pulmonary artery[12-14, 44] of perfused hearts (beating, quiescent, and fibrillating); on the changes in diameter of isolated arterial rings;[10, 15] on the coronary artery inflow under constant or declining pressure in heart-lung or whole animal preparations;[3, 16] on the coronary sinus outflow in heart-lung preparations or the whole animal;[17-22] and on the measurement of the inflow into the coronary arteries, perfused directly from the aorta, by means of the thermostromuhr.[23-25] The clinical, and, to some extent, the experimental aspects of this subject have been reviewed in several recent papers.[26-28, 48]

Despite the variety of methods, each with its own peculiar pitfalls, nearly all investigators agree that these drugs have a vasodilating action on the coronary vessels. The fact remains, however, that alterations in the coronary blood flow in the intact animal may differ significantly in extent and even in direction from what would be anticipated as a result of active changes in the size of the coronary vessels, because of varying degrees of extravascular compression by the contracting cardiac muscle,[29, 31-35] changing cardiac output (mechanical, reflex, and metabolic effects[29, 30]), and alterations of blood pressure per se.[36] These cannot be completely studied in the whole animal by measuring the inflow with the thermostromuhr or by measuring the outflow from the coronary sinus, for these yield only the mean flow; furthermore, the latter has been shown to be subject to serious error.[31, 37, 38]

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It therefore becomes of practical importance to study both the rate of inflow at any given moment, as well as the mean or total inflow into the coronary artery, and to take, simultaneously, an adequate record of the phasic variations of the aortic pressure, using preparations which correspond as nearly as possible to the intact animal. Such experiments have been made possible by the development by Gregg and Green[39] of a method for optically recording, at each instant in the heart cycle, the rate of inflow into a coronary artery, together with the aortic pressure. This paper deals with the application of their method to the study of changes in coronary flow produced by the nitrites and xanthines.

METHOD

Thirteen dogs, weighing from 11 to 23 kg., were anesthetized with morphine (40 mg., given subcutaneously) and either sodium barbital (200 to 250 mg. per kilogram) or sodium pentobarbital (15 to 20 mg. per kilogram), given intravenously. Artificial respiration was started, and the heart was exposed by resection of the left fourth and fifth ribs and suspended in a pericardial cradle. The animal's blood was rendered noncoagulable by the intravenous administration of heparin (75 units per kg.), plus chlorazol fast pink (80 mg. per kg.) or calcomine fast pink 2BL* (120 to 160 mg. per kg.). A cannula was then introduced either into the descending ramus of the

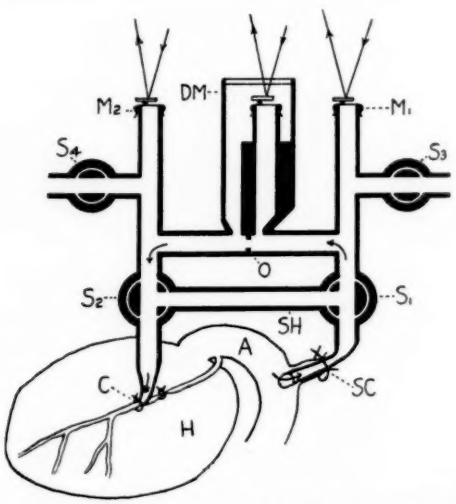

Fig. 1.—Schematic diagram of the apparatus used in measuring the coronary blood flow. *A*, Aorta; *C*, descending ramus of the left coronary artery; *DM*, differential manometer; *H*, heart; M_1 and M_2, pressure manometers; *O*, orifice; S_1, S_2, S_3, and S_4, stopcocks; *SC*, subclavian artery; *SH*, shunt. When flow is being registered the stopcocks are turned so that blood flows from the cannula in the subclavian artery; *SC*, through the orifice, *O*, and thence into the coronary artery, *C*, as indicated by the arrows. The blood, in flowing through the orifice, causes the lateral pressures above and below the orifice to differ; that on the upstream side is the higher. This difference in pressure, which is proportional to the square of the rate of flow, is recorded by the differential manometer, *DM*, which is connected to the system immediately above and below the orifice. The pressure manometers serve to record the animal's blood pressure. When the flow meter (the orifice and differential manometer, taken together, constitute the flow meter) is being calibrated, the blood flowing from the aorta to the coronary artery is directed by the stopcocks S_1 and S_2 through the shunt, *SH*. The calibrating fluid is then directed into the flow meter through stopcock S_3, and its rate of flow measured with a graduate as it flows out through stopcock S_4. The arrows indicate the paths of the light beams used in recording the flow and pressures.

*Courtesy of the Calco Chemical Company, Inc.

left coronary artery or one of its large proximal branches. This cannula was connected, through a flow meter, to a cannula inserted into the aorta by way of the left subclavian or carotid artery, so that the area to be studied was at all times perfused by a pulsatile stream of blood from the animal's own aorta (see Fig. 1). When a branch of the coronary artery was used, the main vessel proximal to the side branch was clamped while records of the coronary flow were being made.

Both intracoronary and intravenous injections were given. For the former, the drugs were dissolved in not more than 0.5 to 2.0 c.c. of Locke's solution, or a similar amount of blood previously withdrawn from the animal. The total dose was given by way of the coronary cannula over a period of approximately ten seconds. At this rate of injection, no significant alterations in the blood pressure in the coronary artery occur. For intravenous injections, larger doses, dissolved in 10 c.c. or more of Locke's solution, were used. Simultaneous records of aortic pressure and coronary flow were taken at frequent intervals prior to injection of the drug and until recovery had occurred. Most of the injections were intracoronary because the smaller dosage allowed more frequent injections.

The flow was recorded by means of the differential manometer and "minute-orifice" meter described by Gregg and Green,[39] with certain modifications.[40, 41] The differential manometer records the rate of flow by deflecting a light beam which is focused on a photokymograph. The meter is calibrated at frequent intervals during an experiment by running fluid through it at known rates of flow and simultaneously recording the deflection of the differential manometer beam. The aortic pressure was registered by a rubber-membrane optical manometer similar to that devised by Gregg.[42] The rate of flow (in cubic centimeters per minute) at any instant is ascertained by comparing the deflection of the differential manometer beam at that instant with the deflections obtained during the above-mentioned calibrations (Figs. 2 and 4). The total flow during any given period was ascertained by measuring the area on the record bounded by the flow curve, the zero flow line, and the ordinates demarcating the beginning and end of the interval. Since the deflection of the differential manometer beam is proportional to the square of the rate of flow, it is necessary, in order to compute the area correctly, to reconstruct the flow curve with a linear ordinate scale. This reconstruction was accomplished by means of the square root extractor devised by Green.[43] (See also Gregg and Green.[39])

RESULTS

Normal Flow Curve.—In order to understand the effects of drugs, it is necessary first to review the characteristics of a "normal" flow curve. Fig. 2*A* may be conveniently used for this purpose. The lowest line records the rate of flow (*FL*), upward movement indicating an increase. The upper lines (*AP* and *CP*) record the aortic pressure on the aortic and coronary sides of the meter. At the end of diastole the rate of flow is rapid, i.e., 53 c.c. per minute, but, with the onset of isometric contraction (*1*), the rate diminishes abruptly to 20 c.c. per minute as a result of the compressing effect exerted by the contracting cardiac muscle. The rate of flow increases during the rise of aortic pressure, but usually decreases slightly in the latter half of systole (see segments *B* and *C*). In this record the rate of flow at the peak of aortic pressure is 34 c.c. per minute, and, at the end of systole (*2*), 33 c.c. per minute. The rate of flow increases rapidly during isometric relaxation and then declines gradually during the latter part of diastole as aortic pressure falls.

Nitrites.—The effect of the intracoronary injection of 3 mg. of sodium nitrite is illustrated in segment *B* of Fig. 2. The rate of flow at the end of diastole (*1*) was 63 c.c. per minute; at the end of isometric contraction (minimal rate of systolic flow), 27.5 c.c. per minute; at the peak of aortic pressure, 52 c.c. per minute; and, at the end of systole (*2*), 48.5 c.c. per minute, despite a decline of aortic pressure from

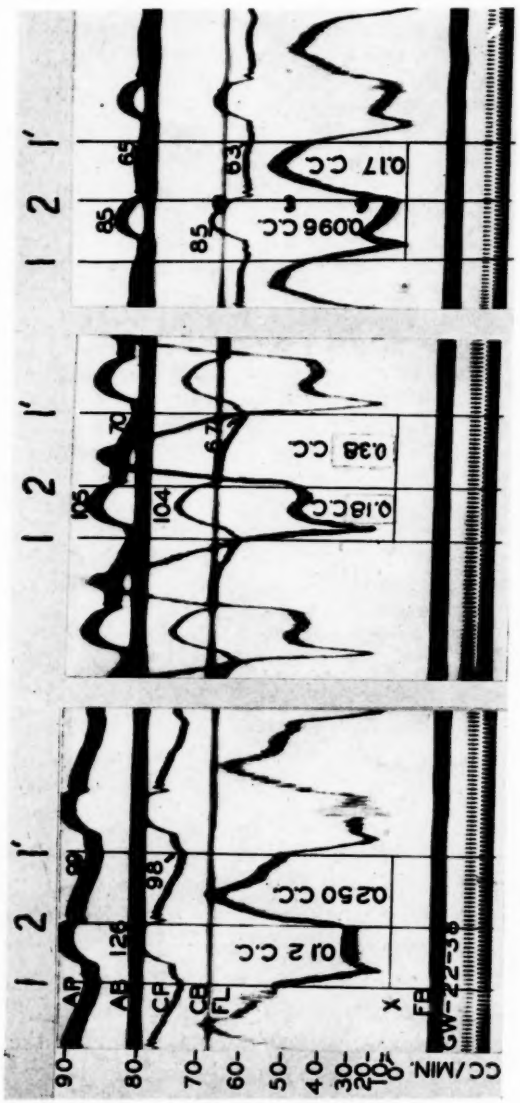

Fig. 2.—Segments of a record showing the effects on blood pressure and coronary flow of injecting 3 mg. of sodium nitrite into the coronary artery. The lowest curve, *FL*, which records the rate of flow at each instant, was made with the differential manometer, *DM*, Fig. 1. Upward movement indicates increased flow. The inked line *X* indicates the position which the upper edge of the flow line *FL* would occupy during zero flow. The rate of flow at any instant may be read from the scale at the left (read to top of the flow line). The two upper curves, *AP* and *CP*, were recorded by means of the two pressure manometers, M_1 and M_2, respectively, of Fig. 1. The pressures, in millimeters of mercury, at the systolic peak and at the end of diastole are indicated by the figures accompanying the pressure records. Segment *A* was taken immediately before the injection of nitrite. Segment *B* was taken 40 seconds, and segment *C*, 7.7 minutes, after the injection of the drug. Time interval, 0.02 second.

126/98 in the control record to 104/67. After 7.7 minutes (segment *C*) the rates of flow had diminished to less than the control values, and the aortic pressure continued to fall.

The figures adjacent to the flow curve record the total flow for the portion of the heart cycle in which they are placed. For instance, in

segment *A* (Fig. 2) the flow during systole (*1 - 2*) was 0.12 c.c., and, during diastole (*2 - 1'*), 0.25 c.c., i.e., in this record, the systolic flow was 32 per cent of the cycle flow. Multiplying these figures by the heart rate (104 per minute) gives a total systolic flow of 12.5 c.c. per minute. Similarly, the flow during diastole was 26 c.c. per minute. For the cycle the total flow was therefore 38.5 c.c. per minute, which corresponds to the average rate of flow obtained by other methods. Thirty-five seconds after the injection of the nitrite (segment *B* of Fig. 2) the systolic flow had increased to 0.18 c.c., and the diastolic flow to 0.38 c.c. Although the average deflection of the flow curve in diastole in segment *B* appears to be almost twice that in segment *A*, the total flow increased only from 0.25 to 0.38 c.c. This is because the deflection of the flow meter beam was nonlinear. (See calibration at the left of the figure.) Because of the increased rate of flow and the increased heart rate, the total systolic flow increased to 19.5 c.c. per minute, the diastolic to 41.5 c.c. per minute, and the total (or average) cycle flow to 61 c.c. per minute.

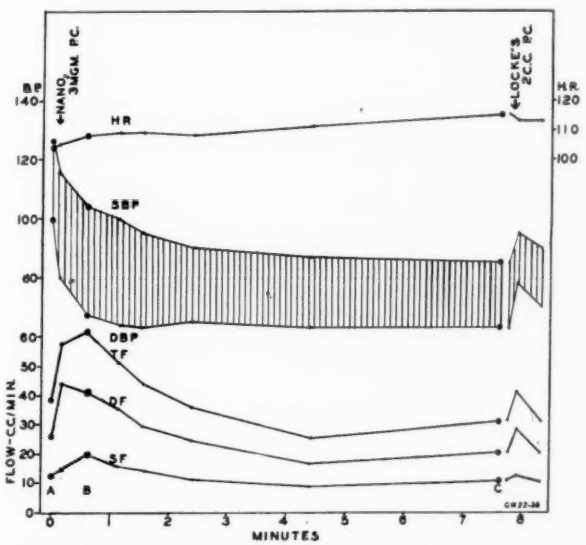

Fig. 3.—Plot of heart rate (*HR*), systolic (*SBP*) and diastolic (*DBP*) blood pressure, total systolic flow per minute (*SF*), total diastolic flow per minute (*DF*), and total cycle flow per minute, *TF* (*SF* + *DF*). Upper scale at left (*BP*) indicates blood pressure in millimeters of mercury. Lower scale at left indicates total flow in cubic centimeters for one minute for all three lines (*SF*, *DF*, and *TF*). Scale at right (*HR*) is heart rate in cycles per minute. Encircled points *A*, *B*, and *C* are from the similarly labeled segments of Fig. 2.

In order to illustrate the successive changes in rate of flow that occurred in this experiment, the data from the control and the seven records which were taken at intervals after the injection of the nitrite are presented in a plot in Fig. 3. The encircled points, labeled *A*, *B*, and *C*, correspond respectively to the similarly labeled segments of Fig. 2. The immediate increase in the flow persisted for 1.5 minutes, when probably because of the decline of aortic pressure, it decreased below

the control value and only very gradually returned toward normal. Early in the course of this work it became apparent that the intracoronary injection of a small quantity of Locke's solution, and, frequently, even of blood, resulted in a momentary increase in coronary flow, and it therefore became necessary to control the effect of an intracoronary injection of a drug by the intracoronary injection of a similar quantity of blood or Locke's solution without the drug. The brief effect of 2 c.c. of Locke's solution is shown at the right of Fig. 3.

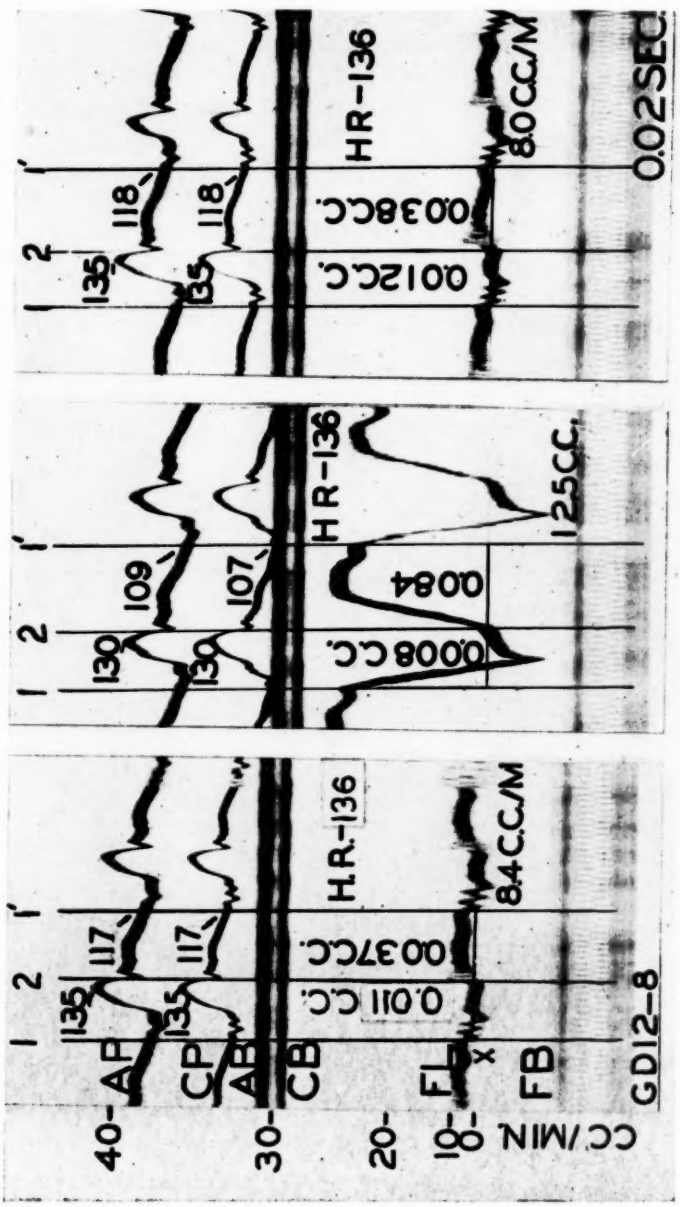

Fig. 4.—Segments of a record illustrating the effects of an intracoronary injection of 5 mg. of theamine (theophylline mono-ethanolamine). *A*, Control; *B*, twenty seconds after injection; and *C*, 5.8 minutes after injection. See Fig. 2 for explanation of lettering.

Xanthines.—As a result of the intracoronary injection of 5 mg. of theamine (Fig. 4, segment *B*) the rate of coronary flow at the end of diastole (*1*) increased from 8.5 to 24.5 c.c. per minute. The minimal rate of systolic flow (at the end of isometric contraction) changed from –5 to –14 c.c. per minute, that at the peak of aortic pressure from 4 to –4 c.c. per minute, and that at the end of systole (*2*) from 2.5 to 4 c.c. per minute. Thus, despite the elevated rate of inflow during diastole (*1*), the rate diminished to a value below zero, so that the drug* actually caused a considerable backflow during most of the ejection phase of systole (*1* – *2*).

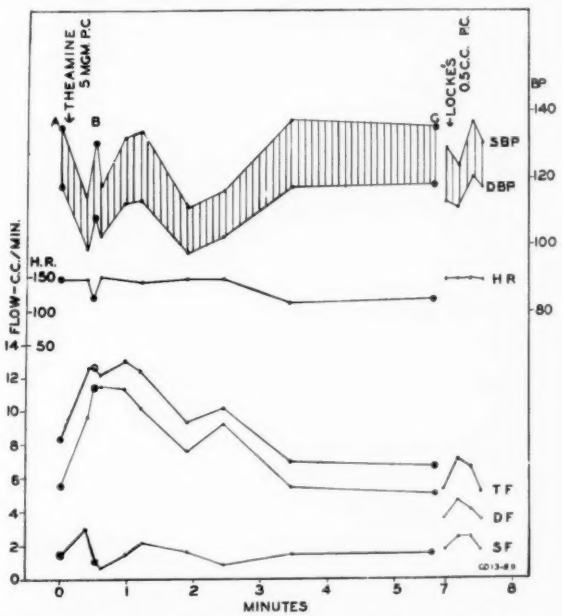

Fig. 5.—Plot of all of the data obtained after an injection of theamine. The encircled points are for the similarly labeled segments of Fig. 4. See Fig. 3 for explanation of lettering.

Fig. 5 is a plot of all of the effects of the drug injection just described. The marked oscillations of the blood pressure cannot be ascribed to the drug, for they were present throughout the experiment, and are probably Traube-Hering waves. The flow during the entire heart cycle and during diastole was increased and remained elevated for about 2.5 minutes, when it declined to values slightly below those of the control record.

Tabulation of Data.—In order to obtain an estimate of the changes in the average rate of flow, but more particularly to allow a statistical analysis of the mechanisms of the action of the drugs, based on their effects on the intramural flow, we measured and tabulated the rates of flow at the four critical points in the heart cycle described above for

*For curves illustrating the effects of intravenous injections of the nitrites and xanthines, see Green.[48]

TABLE

NO.	DRUG	R. A.	DOSE (MG.)	DOG WT.	DOG NO.	REC. NO.	H.R.		S/C		E/C	
							B	A	B	A	B	A
1	No	C	5	13.5	GD. 14	7	158	160	0.35	0.36	0.21	0.21
2	No	V	50	13.5	GD. 14	9	158	154	0.40	0.43	0.20	0.21
3	Ng	C	2	11.4	GW. 9	27	114	118	0.45	0.44	0.36	0.31
4	Ng	V	10	11.4	GW. 9	28	112	122	0.46	0.41	0.32	0.32
5	No	V	100	11.4	GW. 9	29	114	117	0.45	0.35	0.33	0.32
6	No	V	100	23	GW. 12	9	90	100	0.36	0.36	0.27	0.30
7	Ng	C	0.6	23	GW. 12	12	74	82	0.32	0.31	0.27	0.30
8	No	V	100	13	GW. 14	1	212	212	0.45	0.45	0.29	0.34
9	No	V	30	13	GW. 14	2	212	212	0.48	0.48	0.30	0.31
10	No	C	30	13	GW. 14	4	212	212	0.46	0.46	0.27	0.25
11	No	C	30	10.5	GW. 20	20	150	158	0.50	0.50	0.45	0.45
12	No	C	30	10.5	GW. 20	21	154	160	0.50	0.50	0.30	0.38
13	Ng	C	0.3	10.5	GW. 20	22	150	150	0.50	0.50	0.40	0.40
14	Ng	C	1.2	12.5	GW. 22	29	142	146	0.50	0.48	0.36	0.38
15	No	C	20	12.5	GW. 22	33	141	143	0.47	0.47	0.31	0.33
16	No	C	30	12.5	GW. 22	38	104	106	0.45	0.43	0.31	0.32
17	Ng	C	1.2	12.5	GW. 22	40	116	118	0.45	0.45		
18	No	C	30	19	GW. 23	12	86	88	0.37	0.32	0.30	0.28
19	Ng	C	1.2	19	GW. 23	14	71	75	0.38	0.37	0.28	0.30
20	Ng	C	2.4	19	GW. 23	16	76	80	0.36	0.33	0.28	0.27
21	Am	C	5	11.5	GD. 10	2	148	154	0.42	0.43	0.28	0.28
22	Am	C	20	11.5	GD. 10	7	150	150	0.40	0.40	0.28	0.30
23	Am	V	20	11.5	GD. 10	8	133	133	0.35	0.35	0.30	0.32
24	Am	C	0.9	23	GD. 11	12	135	140	0.48	0.47	0.32	0.32
25	Am	C	1.8	23	GD. 11	15	139	146	0.49	0.46	0.31	0.26
26	Am	C	9	23	GD. 11	16	150	152	0.51	0.46	0.30	0.28
27	Am	V	48	23	GD. 11	19	150	162	0.45	0.44	0.27	0.27
28	Th	C	20	15.5	GD. 12	4	146	154	0.44	0.44	0.27	0.26
29	Th	V	20	15.5	GD. 12	7	137	146	0.41	0.40	0.25	0.24
30	Th	C	5	15.5	GD. 12	8	136	136	0.41	0.41		
31	Th	V	40	15.5	GD. 12	10	139	170	0.37	0.40	0.20	0.21
32	Am	C	5	15.5	GD. 12	13	138	136	0.39	0.39	0.25	0.23
33	Am	V	45	15.5	GD. 12	16	150	167	0.37	0.38	0.26	0.23
34	Am	C	5	15.5	GD. 12	18	145	145	0.40	0.40	0.26	0.24
35	Th	C	2.5	15.5	GD. 12	19	140	140	0.39	0.39	0.22	0.26
36	Am	V	50	15.5	GD. 12	20	148	156	0.41	0.41	0.24	0.23
37	Th	C	5	13.5	GD. 14	1	158	158	0.40	0.41	0.24	0.24
38	Th	C	5	13.5	GD. 14	3	162	161	0.40	0.39	0.27	0.24
39	Th	V	50	13.5	GD. 14	5	162	168	0.38	0.41	0.20	0.25
40	Am	C	1	15.5	GJ. 5	2	191	193	0.42	0.34	0.26	0.28
41	Am	C	1	15.5	GJ. 5	4	184	186	0.42	0.37	0.27	0.24
42	Th	C	1	20.5	GD. 17	3	140	153	0.45	0.43		
43	Th	C	4	20.5	GD. 17	4	140	140	0.48	0.43		

Table of data obtained after all experimentally satisfactory injections of the drugs. NO_2, Sodium nitrite; NG, nitroglycerine; AM, aminophyllin*; TH, theamine†; R.A., route of administration; C, injected into coronary artery; V, injected intravenously; Dose, in milligrams; Dog Wt., in kilograms; Rec. No., serial number of the record; H.R., heart rate in beats per minute; S/C, systole cycle ratio; E/C, ejection cycle ratio; B.P., blood pressure in millimeters of mercury; B, before giving the drug; A, after giving the drug; S, systolic blood pressure measured at the peak of the aortic pressure curve; P, pressure at the onset of protodiastole; D, diastolic pressure measured at the

*Theophylline-ethylenediamine, courtesy G. D. Searle & Co.

†Theophylline mono-ethanolamine, courtesy Eli Lilly Co.

all injections included in this series of experiments. The data (Table I) are from a control record and a record showing approximately the maximum effect of the drug, omitting consideration of the first ten to fifteen seconds after intracoronary injections in order to avoid the immediate effects of the injection. Two of the above critical points,

I

B. P.						FLOW							
B			A			I		P. S.		E. S.		E. D.	
S	P	D	S	P	D	B	A	B	A	B	A	B	A
84	83	62	74	73	50	0.0	6.0	11.5	10.0	0.0	0.0	16.5	21.0
132	130	113	94	93	80	5.0	2.0	9.0	10.0	9.0	10.0	12.5	17.5
94	82	69	82	73	58	−10.5	− 9.0	17.5	20.5	10.0	9.0	35.5	37.0
95	88	70	100	86	64	5.0	5.0	37.0	30.5	32.5	23.5	52.0	58.0
96	84	60	82	70	45	0.0	20.5	37.0	42.0	28.0	27.0	51.5	55.0
105	80	60	88	64	45	10.0	20.5	20.5	31.0	18.5	10.0	47.0	52.0
97	90	67	89	80	51	9.0	14.5	22.5	24.0	11.0	9.0	44.0	46.0
124	122	92	86	80	55	−13.5	−12.0	17.0	23.5	0.0	0.0	29.0	35.0
120	115	96	117	110	90	−10.0	−10.0	23.5	23.5	0.0	0.0	35.0	32.5
122	105	98	112	98	90	0.0	12.0	20.0	31.5	0.0	22.5	29.0	53.0
114	94	68	105	86	59	20.5	21.0	31.5	32.5	20.5	21.0	44.5	46.0
104	83	62	95	79	54	27.0	23.5	32.5	34.0	20.0	16.5	46.0	44.0
94	78	58	90	67	55	25.5	29.0	27.5	29.0	16.0	16.0	46.5	46.5
95	80	60	92	76	42	0.0	28.5	20.0	38.0	20.0	37.0	38.5	48.0
95	82	60	89	73	48	16.0	30.0	26.5	36.5	15.0	24.5	45.0	54.0
126	126	98	104	95	67	20.0	27.5	33.5	51.0	33.0	48.5	53.0	63.0
88	85	65	84	70	53	11.0	22.0			24.0	34.5	47.5	60.0
140	135	90	140	136	95	30.0	18.0	28.0	27.0	36.0	31.0	42.0	40.0
123	117	75	116	107	70	25.0	22.0	34.5	31.0	34.0	31.0	30.0	35.0
119	110	68	118	109	64	10.0	10.0	31.0	30.0	30.0	30.0	31.0	30.0
130	125	103	125	122	100	−15.0	−15.0	17.0	19.0	12.0	12.0	28.0	28.0
82	80	55	79	65	41	−16.0	−12.0	8.5	10.0	8.0	8.0	31.0	29.0
70	68	42	90	82	42	− 8.0	−15.0	16.0	20.0	8.0	8.0	27.0	32.5
96	90	67	100	96	70	8.0	8.0	22.0	23.5	17.5	22.0	33.5	42.0
95	90	70	96	93	69	8.0	12.0	19.5	20.5	13.0	25.0	30.0	42.0
92	88	66	97	94	68	10.0	0.0	21.5	29.5	17.0	30.0	31.0	51.0
94	90	70	92	89	63	8.0	13.0	25.5	31.5	22.0	25.0	34.0	41.5
126	122	110	127	122	107	− 2.5	−15.0	3.0	5.5	2.5	6.5	6.0	22.5
109	107	92	113	110	95	0.0	0.0	4.5	4.5	2.5	3.5	5.5	8.5
135	132	117	130	126	107	− 5.0	−14.0	4.0	−4.0	2.5	4.0	8.5	24.5
106	104	90	111	109	96	0.0	0.0	3.5	2.0	2.5	0.0	5.0	7.0
101	98	81	100	96	80	− 2.5	− 6.5	4.5	0.0	2.0	0.0	6.5	14.0
110	102	90	107	90	76	− 3.5	0.0	5.0	3.5	3.0	2.5	7.0	9.5
95	91	77	102	97	83	− 4.0	− 7.0	3.0	3.5	0.0	3.5	7.0	10.0
98	94	82	101	98	81	− 3.0	− 6.0	4.0	0.0	2.0	0.0	6.0	9.5
99	96	81	95	90	79	− 3.0	− 5.0	5.0	4.0	2.5	2.5	6.5	8.5
100	98	82	100	97	80	0.0	0.0	7.5	8.0	5.0	5.0	12.5	13.5
96	92	77	98	94	68	− 2.0	− 4.0	9.0	10.5	4.0	5.5	14.0	25.0
100	98	80	92	87	65	1.5	2.0	9.0	4.0	2.5	4.0	12.5	18.0
116	112	99	115	115	95	−12.0	−33.0	11.0	5.0	16.0	15.0	20.5	41.5
130	124	103	125	118	95	− 2.5	−16.0	12.5	8.0	13.5	12.0	30.0	38.0
85	82	64	80	77	60	15.5	13.0	26.0	19.0	17.5	15.5	39.0	44.0
72	69	58	73	71	60	12.5	0.0	25.5	19.0	18.0	25.0	38.0	43.5

onset of isometric contraction; Flow, coronary rate of flow in cubic centimeters per minute; I, minimal rate of flow at approximately the end of isometric contraction; P.S., rate of flow at peak of aortic pressure; E.S., rate of flow at end of systole; E.D., rate of flow at end of diastole. The G.W. animals were anesthetized with sodium barbital, the G.D. animals with sodium pentobarbital. These two series of animals were also used for other drug injections (see Green, Boyer, Wegria, and Kent).[41]

i.e., the end of systole, corresponding to the peak of the peripheral coronary pressure curve,[32] and the end of diastole, are those at which, according to Gregg and Green,[39] the rate of change of volume elastic and myocardial compression forces are minimal under normal conditions. The rate of inflow at these points in the cycle, therefore, most nearly represents intramural flow. We can, accordingly, use changes in the rate of inflow at the end of diastole as an index of the degree of

contraction or relaxation of the coronary vessels, and there is relatively little danger that this index will be affected by extravascular compression. Similarly, changes in the rate of inflow in the latter part of systole may be regarded as reflecting variations of myocardial compression, plus changes in the caliber of the coronary vessels. Under the action of certain drugs, however, the peak of the peripheral coronary pressure curve is advanced from the end of systole to approximately the peak of the aortic pressure curve.[48] Therefore the resistance to flow may actually be increased during most of systole as a result of the action of the drug, but it may be decreased at the very end of systole. Such a change in the form of the resistance curve occurs rather regularly with epinephrine,[41] and was observed in two experiments with the xanthines in which the peripheral coronary pressure was measured. In order to evaluate this possible change in dynamics, we have measured the flow at the third critical point, namely, the peak of the aortic pressure curve. The fourth critical point which we have measured and tabulated in order to give a further idea of the extent of the reduction in flow caused by extravascular compression is the inflow at the end of isometric contraction (minimal systolic flow).

Comparison of Nitrites and Xanthines.—The data from Table I are summarized in Tables II and III. Injections which, either because of the smallness of the dose or nonreactivity of the animal, resulted in no appreciable change in flow or blood pressure have been eliminated. The difference between the nitrite and xanthine experiments with respect to the average control pulse pressure and heart rate may be ascribed to a difference in anesthetics or to slight differences in the operative technique which was used in the two groups of experiments.

The effects of the drugs have been expressed as the average of the per cent change. Mean blood pressure, calculated as the arithmetical mean of the systolic and diastolic blood pressures, tended to be lowered by the nitrites. This effect was greater the larger the dose, and was, therefore, more marked with the larger intravenous injections. The xanthines had, in general, no significant effect on mean blood pressure. The larger doses of the latter group of drugs, particularly the intravenous injections, increased the pulse pressure moderately and the heart rate slightly more than did the nitrites. Both intracoronary and intravenous injections of the nitrites tended to decrease the systole-cycle ratio and to increase the ejection-cycle ratio slightly, whereas the intracoronary injections of the xanthines tended slightly to decrease both ratios, but, because of the variability of the effects, as shown by the magnitudes of the sigma values, these small differences are perhaps not significant.

In order to separate the changes in peripheral coronary resistance from the effect of blood pressure variations caused by the drugs, we

TABLE II

		NIT. COR.	XANT. COR.	NIT. VEIN	XANT. VEIN
No. Exp.		10	14	5	7
M.B.P.	Av. Control	86.5	91	94.7	88.1
	Av. % change	−11.7	−1.1	−22.1	−1.2
	σ (%)	8	6.5	15	8
P.P.	Av. Control	31	20.9	31.4	20.4
	Av. % change	+14.8	+12	+1.3	+29
	σ (%)	16	21	19	34
H.R.	Av. Control	136.5	149	137	153
	Av. % change	+2.8	+1.5	+2.8	+5.9
	σ (%)	2.2	3	4	8
S/C	Av. Control	0.445	0.435	0.425	0.391
	Av. % change	−1.3	−4.6	−5.6	+2
	σ (%)	2.2	5.7	10.5	3.6
E/C	Av. Control	0.316	0.273	0.282	0.246
	Av. % change	+2.2	−4	+6.4	+0.4
	σ (%)	3.2	14.5	7.1	10
D.I.	Av. Control	0.563	0.308	0.560	0.222
	Av. % change	+50	+82	+63	+45
	σ (%)	28	76	32	19
E.S.I.	Av. Control	0.151	0.106	0.200	0.069
	Av. % change	+38	+19	+2	+2
	σ (%)	43	68	32	46
P.S.I.	Av. Control	0.226	0.140	0.236	0.107
	Av. % change	+37	−9	+47	−15
	σ (%)	26	25	42	23
E.S.C.	Av. Control	0.412	0.209	0.360	0.152
	Av. % change	+39	+120	+98	+62
	σ (%)	18	150	38	18
P.S.C.	Av. Control	0.337	0.180	0.324	0.115
	Av. % change	+56	+163	+89	+132
	σ (%)	37	151	50	60

Summary of data from Table I. Nit. Cor., averages of results of injection of sodium nitrite and nitroglycerine into the coronary artery; Nit. Vein, same for injections into jugular vein; Xant. Cor., averages of results of injection of theamine and aminophyllin into the coronary artery; Xant. Vein, same for injections into jugular vein; No. Exp., number of records in each of above groups included in ascertaining the average; M.B.P., mean blood pressure; P.P., pulse pressure (aortic systolic pressure, minus aortic diastolic pressure); H.R., heart rate (beats per minute); S/C, systole-cycle ratio; E/C, ejection-cycle ratio; D.I., diastolic flow index; E.S.I., flow index at end of systole; P.S.I., flow index at peak of aortic systolic pressure; (all indices calculated as flow, in cubic centimeters per minute, divided by pressure, in millimeters of mercury; E.S.C., difference between diastolic index and index at end of systole; P.S.C., difference between diastolic index and index at peak of aortic pressure; Av. Control, average of the control values; Av. % change, average of the individual percentage change calculated as:

$$\frac{\text{reading before giving drug} - \text{control reading}}{\text{control reading}} \times 100$$

σ (%) = square root of sum of the squares of the differences between the average percentage change and the individual percentage changes, divided by the number of observations (see Rider,[30] p. 88). Note: Margin numbers 9, 13, 18, 19, 20, 30, and 37 of Table I were omitted in preparing this table.

have calculated an index of flow, i.e., the ratio of the rate of flow in cubic centimeters per minute to the simultaneously existing aortic pressure in millimeters of mercury. Such ratios have been calculated for the peak of aortic systolic pressure (P.S.I.), for the end of systole (E.S.I.), and for the end of diastole (D.I.). The significance of these

ratios depends, of course, upon whether or not the flow shows a linear correlation with pressure. We believe that it is reasonable to assume that it does, over the range of pressure change which occurred. Assuming that at the end of diastole the vascular bed was not being affected by active myocardial extravascular compression, the percentage change in the diastolic index (D.I.) will indicate the effect of the drug on the coronary vessels which control blood flow, i.e., an increase in the ratio, expressed as + per cent, indicates active vasodilatation, and vice versa. It is apparent from Table II that both groups of drugs and both routes of administration increased the D.I. and that, furthermore, the magnitude of the effect was, on the average, comparable among the four groups.

It may be assumed that, if no other factors intervened, the percentage changes in the indices at the peak of aortic systolic pressure (P.S.I.) and at the end of systole (E.S.I.) would be the same as for the diastolic index (D.I.). It is apparent from Table II that the increase in both systolic indices was, in general, less than that in the diastolic indices for both groups of drugs and both routes of administration. The failure of the E.S.I. to increase in proportion to the D.I. was most noticeable when the two groups of drugs were given intravenously, but was also readily apparent after intracoronary injection of the xanthines. The difference between the effect of the xanthines and nitrites on the P.S.I. was striking; on the average, the index was decreased as a result of giving the former, whether intravenously or into the coronary artery, whereas the nitrites increased the P.S.I. almost as much as the D.I.

These results on the indices suggest that the intracoronary and intravenous injection of the xanthines and the intravenous injection of the nitrites produce a dual effect. One is a decrease in peripheral resistance throughout the cycle, caused by dilatation of the vessels which control coronary flow, and the other is an increase in the resistance to flow during systole, brought about by an increase in the extravascular compression exerted by the contracting myocardium. To view this latter effect in another way, we have subtracted the index at the peak of aortic pressure (P.S.I.) and that at the end of systole (E.S.I.) from the diastolic index (D.I.) in each record. These differences (P.S.C. and E.S.C., respectively) represent the extent of the reduction of the vascular bed caused by systole. The percentages of increase in these differences which were caused by the drugs are tabulated in Table II. The extent of the reduction of the vascular bed at the end of systole (E.S.C.), as calculated by this method, was, on the average, one and a half times as large after intravenous injection of the xanthines and almost three times as large after intracoronary injection of the xanthines as that caused by intracoronary injection of the nitrites. The reduction caused by intravenous injection of the nitrites was of the order of twice that caused by intracoronary injection of nitrites. The

reduction of the extent of the vascular bed at the peak of the aortic pressure (P.S.C.) caused by the xanthines was, on the average, two to three times that brought about by the nitrites.

TABLE III

DRUG	ROUTE	TOTAL FLOW C.C./MIN.			TOTAL FLOW ÷ BY M.B.P.		
		BEFORE	AFTER	CHANGE %	BEFORE	AFTER	CHANGE %
Nitrite	C	28.6	34.5	20.0	0.33	0.45	36.5
Xanthine	C	16.7	24.0	44.0	0.18	0.27	46.0
Nitrite	V	20.8	22.8	9.6	0.22	0.31	45.0
Xanthine	V	10.9	13.1	20.0	0.12	0.15	22.5

Average change in total flow per minute and average change in total flow per minute per millimeters of mercury, calculated from data given in Table I. Nitrite includes sodium nitrite and nitroglycerine; Xanthine includes theamine and aminophyllin; C, injected into coronary artery; V, injected into jugular vein; Before, average control value; After, average value at the instant of the maximum effect of the drug; $\%\ \text{change} = \frac{\text{after} - \text{before}}{\text{before}} \times 100.$

It has been our experience that a fairly close approximation to the total (or average) flow per minute is obtained by adding the product of the rate of flow at the end of diastole times the diastole-cycle ratio to the product of the rate of flow at the end of systole times the systole-cycle ratio. The averages of the data on the total flow per minute calculated in this way, and on the percentage change of the total flow produced by the drugs (for the same experiments that are analyzed in Table II) are presented in Table III. The xanthines apparently caused a greater increase than the nitrites, by both routes of administration, but the increase in terms of actual cubic centimeters was not very large for the intravenous injections of either group of drugs. When, however, as in the right half of the table, the decline of aortic pressure is taken into account, the effects of the two groups of drugs are more nearly comparable.

DISCUSSION

The interest of the therapeutist in this subject will lie in the question whether these drugs are capable of producing a favorable relationship between the work of the heart and the coronary blood flow. Although the cardiac output was not directly measured in these experiments, the behavior of the mean blood pressure and pulse pressure makes it seem likely that the nitrites materially decrease the work of the heart, whereas the xanthines have no such action, or may even increase the work. Furthermore, it has been pointed out in the description of the data on these experiments that the xanthines appear to exert a stimulant action on the myocardium. Under such circumstances it may not be justifiable to attribute vasodilatation solely to the action of the drug, for the increased vigor of contraction may, in itself, by virtue of increased liberation of metabolites, be in part responsible for the vasodilatation. The latter mechanism of increasing coronary blood flow may be considered ineffective from the point of view of enhancing coronary reserve.

Starr, et al.,[45] found evidence that theophylline increased cardiac output without increasing the size of the heart; they interpreted this to indicate increased vigor of contraction or "tone." They also found that the xanthines increased cardiac work without significantly changing the heart rate and with but slight elevation of the blood pressure, whereas the nitrites tended slightly to decrease both the cardiac work and blood pressure. The available information suggests, then, that the actions of these drugs are similar in the anesthetized dog and in man.

SUMMARY AND CONCLUSIONS

The effect of intracoronary and intravenous injection of nitrites and xanthines on the flow of blood from the aorta into a coronary artery was studied in anesthetized dogs by means of a new type of optically recording flow meter.

These two groups of drugs increase the diastolic coronary flow, both absolutely and relative to the aortic head of pressure; this demonstrates dilatation of the vessels which control coronary flow. With intracoronary injection, the xanthines appear at times to exert a stimulant influence on the myocardium. With intravenous injection of both groups of drugs, the increased flow is caused more by augmentation of flow in diastole than in systole. In the case of the xanthines this is probably in part the result of the myocardial stimulant action. With both, changes in the dynamics of the circulation probably play a part; the net effect is an increase in the extravascular compression force exerted by the contracting myocardium.

Changes in cardiac output and systemic peripheral resistance, particularly after administration of the xanthines, complicated the observations so that it is not possible to state definitely whether the increase in flow was in all cases effective in increasing the nutrition beyond what was required by changes in the external work performed by the heart. The nitrites, on the other hand, tended to increase coronary flow at the same time that they decreased the blood pressure and cardiac work.

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THE RELATIONSHIPS OF LEAD I, CHEST LEADS FROM THE C_3, C_4, and C_5 POSITIONS, AND CERTAIN LEADS MADE FROM EACH SHOULDER REGION: THE BEARING OF THESE OBSERVATIONS UPON THE EINTHOVEN EQUILATERAL TRIANGLE HYPOTHESIS AND UPON THE FORMATION OF LEAD I

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SINCE our first demonstration of the diagnostic value of chest leads in acute myocardial infarction,[1] we have been interested in the relations between the limb and chest leads. As long as we used only one anterior chest position (the apex), these relations seemed capricious. Some patients with a normal precordial lead showed abnormalities in Lead I, whereas many with a normal Lead I had abnormalities in the precordial lead. However, when we began to take chest leads from the C_3, C_4, and C_5 positions and studied the relations of these multiple chest leads to Lead I, it quickly became apparent that the relationships were not so capricious as at first they had seemed to be. When CF_3 was abnormal and CF_5 normal, Lead I was usually normal. However, when CF_5 was abnormal, Lead I tended to be abnormal. Moreover, Lead I tended to resemble Lead CF_5 except for the fact that its deflections were likely to be smaller. *A* and *B* in Fig. 1 are examples of electrocardiograms which show the lack of correlation between abnormalities in Leads I and CF_3 and the rather striking correlation often observed between abnormalities in Leads I and CF_5. Although this correlation is far from perfect, it is too close to be a coincidence.

After we had studied the relationships between Leads I and CF_5 in a number of cases, it occurred to us that CR_5 might show an even better correlation with Lead I than did CF_5, because one variable would be eliminated, namely, the position of the right arm electrode. When Leads I and CF_5 were taken, this electrode was placed on the right arm for one lead and on the left leg for the other (two points which differ in potential) and this difference was recorded in Lead II; whereas, when Leads I and CR_5 were taken this electrode was placed on the right arm in both cases. When this point was tested, our supposition was borne out (Fig. 1*C*). There was a much closer correlation between the abnormalities in Leads I and CR_5 than between those in Leads I and CF_5. There were still some exceptions which will be discussed below.

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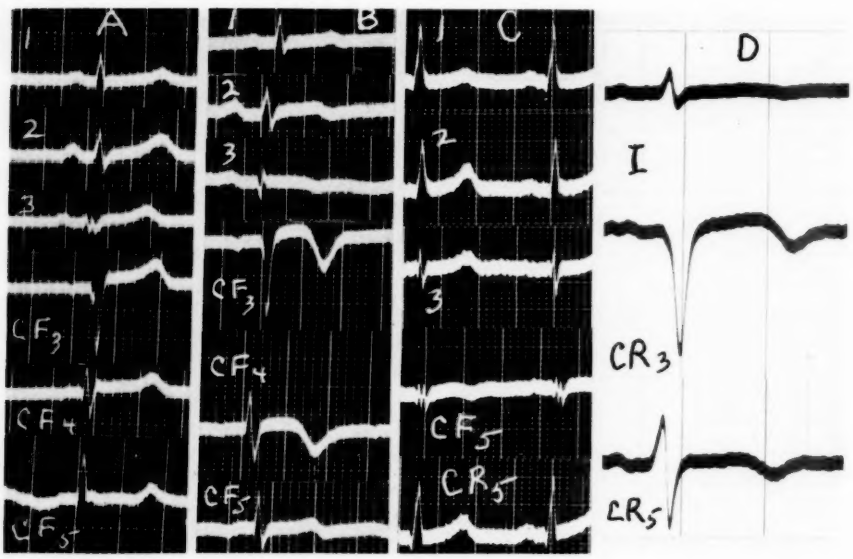

Fig. 1.—*A*. Similarity between contour of ventricular complexes in Leads I and CF_5. No resemblance between the QRS complexes of Leads I and CF_3. *B*, Same patient after a second attack of acute coronary occlusion. The similarity of contour in Leads I and CF_5 persists; both have developed a slightly diphasic T wave. There is no resemblance, either of QRS complexes or T waves, between Leads I and CF_3. The QRS complex of Lead CF_3 is somewhat like that of CF_5 and Lead I, but the T wave, which resembles that of CF_5, is totally unlike those of Leads I and CF_5. *C*, In this case CF_5 is unlike Lead I, whereas CR_5 resembles Lead I (See text for explanation). *D*, The ventricular complexes of Leads I and CR_5 are similar, although the deflections in CR_5 are much larger. There is no resemblance between the QRS complexes of Leads I and CR_3 (film speed, 75 mm. per second).

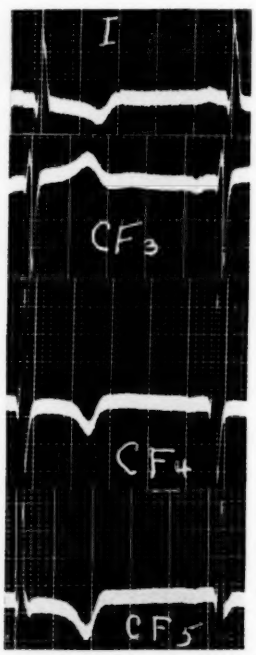

Fig. 2.—Leads I, CF_3, CF_4, and CF_5. This is the pattern of chest leads in which the ventricular complexes of Leads I and CF_4 may show some resemblance. It may occur when CF_4 follows the pattern of CF_5 more closely than that of CF_3.

As in the case of CF_3, no correlation was observed between abnormal patterns of Leads I and CR_3 (Fig. 1*D*). As far as the C_4 position was concerned, an abnormality which appeared at C_4 and C_3, but not at C_5, did not tend to be reflected in Lead I (Fig. 1*B*). However, when an abnormality at C_4 was associated with an abnormal pattern at C_5, Lead I also tended to be abnormal (Fig. 2). This is the explanation for the seemingly capricious relationship between leads from the apex or the C_4 position and Lead I.

The close correlation between Leads I and CR_5, and the lack of correlation between Leads I and CR_3 seemed to indicate that Lead I was being affected by the electrical activity of one part of the ventricular muscle much more than by the rest of this structure. In searching for an explanation of these relationships two possibilities occurred to us: (a) If the Einthoven equilateral triangle hypothesis were even approximately correct, it would mean that some electrical change was being picked up at the C_5 position which influenced Lead I by affecting the potential in both arms and that an electrical change was being registered through the C_3 position which did not produce a discoverable effect on Lead I because it did not materially change the potential in either arm. (b) The Einthoven hypothesis may not account fully for the phenomena which are observed; a certain portion of the ventricle which registers its effects at the C_5 position may be causing a predominant change in potential in one arm without necessarily producing such changes in potential in the other extremities, as would be required by the Einthoven hypothesis. Probably no one would question the physical principles on which the Einthoven equilateral triangle hypothesis is based, but some of the assumptions which underlie its applicability to the human body are open to serious question. It is not necessary here to recapitulate the arguments pro and con, except to mention the work of Eyster, Maresh, and Krasno,[2] and Katz and Korey,[3] who have pointed out that there are marked differences in the conductivity of various body tissues. Their observations throw doubt upon the validity of the fundamentally important assumption of Einthoven that body tissues function as a homogeneous fluid conductor.

In order to investigate the above two possibilities, we attempted to devise a method of studying potential changes separately in the right arm and left arm. The method of Wilson, Johnston, Macleod, and Barker[4] for recording what they regard as the potential of a single area on the body could not be used, because it assumes the complete validity of the Einthoven equilateral triangle hypothesis, i.e., the hypothesis which we are attempting to test.

Many different procedures were employed, but, in most of them, the guiding principle was the study of the differences in potential which developed along lines extending more or less radially from the heart. It was thought that if electrodes could be placed along such a line, the changes in potential should take the same direction under all of them,

but that they might be greatest under the one nearest the heart. If such proved to be the case, one would be in a position to discover the directions of the potential changes in the extremities, even if deviations from the resting potential could not be measured quantitatively by such a procedure.

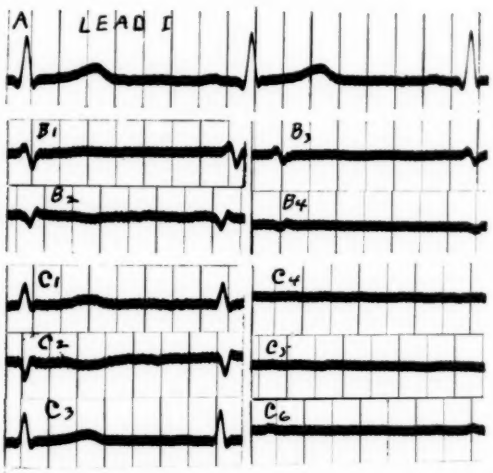

Fig. 3.—Various leads from a normal subject. The special leads in this and all other figures are designated so that positivity of the area mentioned first is represented by an upward deflection. *A*, Lead I. B_1 and B_2: Leads from front and back of chest, respectively (about 2 inches from left arm), paired with the left forearm. B_3 and B_4: Similar leads on the right side. C_1: A lead from as high as possible in the left axilla, paired with the left forearm. C_2: A lead from the top of the left acromial process, paired with the left forarm. C_5: A lead on the right side, made in the same way as C_1. C_3: A lead from high in the left axilla to the tip of the left acromial process. C_6: A similar lead on the right side. All these leads on the left side show far larger ventricular deflections than those on the right side. B_2 and B_4 are almost inverted images of B_1 and B_3, respectively. The same is true of C_1 and C_5. Note the similarity in contour (except for size of deflections) among C_1 (left axilla to left forearm), C_3 (left axilla to left shoulder), and Lead I.

Considerable difficulty was encountered in the practical application of such a method. It quickly became apparent that marked differences existed between the electrical fields of the right and left upper parts of the body; only small differences in potential tended to develop between adjacent areas on the right side, whereas there were often very large differences in potential between comparably situated areas on the left side (Fig. 3). Morever, it was noted that, if one electrode were placed on an arm and the other on the front of the chest near the root of the arm, a tracing was obtained in which the deflections were likely to be opposite in direction from those which were registered when the electrode on the front of the chest was moved to a comparable point on the back (Fig. 3, B_1 and B_2, B_3 and B_4). It was obvious that both of these patterns could not represent the direction of the potential changes in the arm.

Among the earlier leads employed was one in which the left arm electrode was placed as high as possible in the axilla, between the arm and its attachment to the body, and the right arm electrode was placed

on the forearm of the same side. The ventricular deflections recorded on the right side were often so small as to be unrecognizable (Fig. 3, C_4), but on the left they were sometimes almost half as large as those of Lead I (Fig. 3, C_1). The thing which excited our interest was the fact that the general pattern of such a lead on the left side was likely to resemble that of Lead I. We then studied the tracing obtained on the left side by keeping the right arm electrode on the forearm and moving the left arm electrode directly across the root of the arm to the top of the acromion. In such a tracing the deflections were opposite in direction from those of the axilla-arm lead, and usually a little smaller (Fig. 3, compare C_1 and C_2).

It seemed from these observations that a lead made across the attachment of the arm from the axilla (left arm electrode) to the top of the shoulder (right arm electrode) should be nearly twice as large as one made from the left axilla to the left forearm, and that it should still retain its resemblance to Lead I (Fig. 3, C_3). This proved to be the case. An extensive study was then made of these axilla-shoulder leads in both upper extremities. The most important facts which developed as a result of these studies were the following:

1. The ventricular complexes in the left shoulder electrocardiogram are usually astonishingly large, considering the fact that the electrodes are paired across the attachment of the arm, whereas those in the right shoulder electrocardiogram are very small (Fig. 3, C_3 and C_6). There are certain exceptions to these general rules: (a) patients with left ventricular hypertrophy or hypertension may have fairly large deflections in the right shoulder lead (Fig. 4, A_1 and E_5). However, they are nearly always smaller than those in the left shoulder lead, for these also tend to be larger than normal.* (b) Patients with bundle branch block often have large deflections in the right shoulder lead; some are even larger than those from the left side (Fig. 4 B_1 and B_2). (c) Persons with long chests and vertically placed hearts may show minimal deflections in the left shoulder lead; they are sometimes little, if any, larger than those obtained from the right shoulder lead (Fig. 4, C_1 and C_2). (d) Patients with anterior infarction may show extremely small QRS deflections in leads from the left shoulder region (Fig. 4, D_2).

2. When electrodes are applied in the manner described above, the ventricular complexes obtained in leads from the left side look very much like those of Lead I (Fig. 3, Lead I and C_3; Fig. 4, A_2 and A_3, E_1 and E_2); whereas those obtained in leads from the right side usually bear no resemblance to Lead I. The principal exceptions, which are likely to fail to show a resemblance between Lead I and the left shoulder lead, are the last three named in the preceding paragraph (Fig. 4*B*, *C*, and *D*).

*The electrical activity of the left shoulder region in certain cases of hypertension is so great that ventricular deflections of considerable size may be recorded across the left arm 2 inches from the shoulder (Fig. 4, E_5).

3. The average size of the auricular deflections is about the same in the right and left shoulder electrocardiograms. Sometimes they are larger on the right, and sometimes on the left (Fig. 5).

These observations are difficult to account for on the basis of Einthoven's equilateral triangle hypothesis. If, as he suggested, the

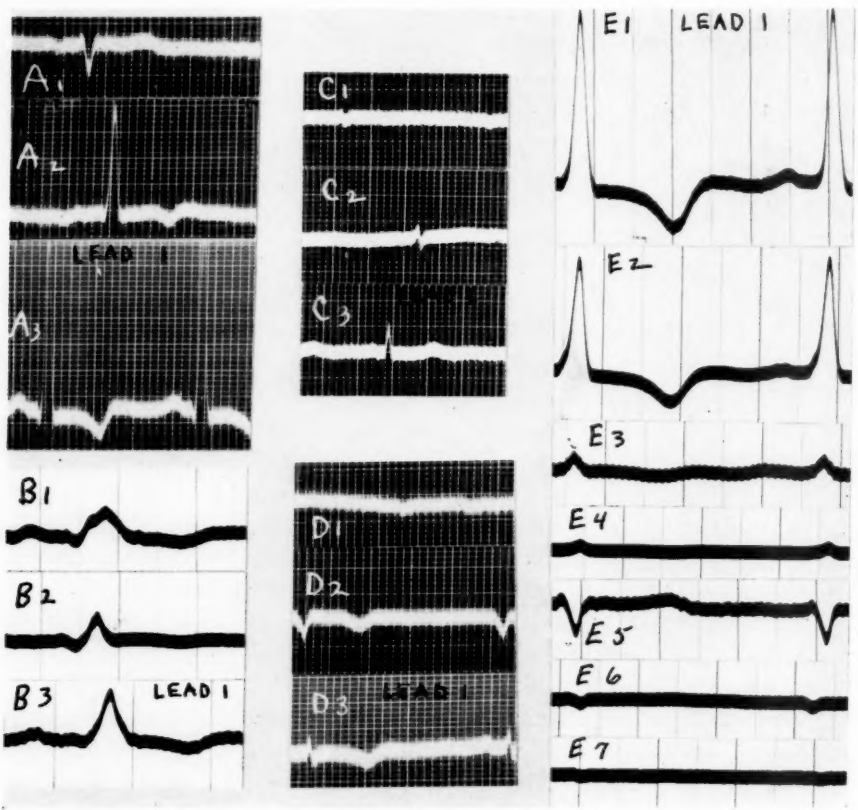

Fig. 4.—*A*, Patient with hypertension. A_1: Lead from right axilla to right shoulder. A_2: Lead from left axilla to left shoulder. A considerable difference of potential may develop across the root of the right arm in cases of hypertension, but, as in this case, much larger deflections are usually recorded across the root of the left arm. The ventricular complexes in the lead from the left side resemble those of Lead I (A_3). *B*, Patient with left bundle branch block. B_1: Right shoulder-axilla lead. B_2: Left axilla-shoulder lead. B_3: Lead I. In cases of bundle branch block the electrical activity about the right shoulder may be as great as or greater than that on the left side. Under these circumstances the contour of the tracing in the lead across the left arm often fails to resemble closely that of Lead I (Film speed, 75 mm. per second). *C*, Patient with long chest and vertically placed heart. C_1: Right shoulder-axilla lead. C_2: Left axilla-shoulder lead. C_3: Lead I. The electrical activity about the left shoulder is little greater than that on the right side. Compare C_2 with A_2 and E_2, all of which were made with the electrodes in similar positions. *D*, Patient with healed anterior infarction. D_1: Right axilla-shoulder lead. D_2: Left axilla-shoulder lead. D_3: Lead I. The QRS complex in the lead across the root of the left arm is represented solely by a small negative deflection. This does not dominate the QRS wave of Lead I, although the T waves are similar in the two leads. *E*, Patient with hypertension and left ventricular hypertrophy. E_1 is Lead I. E_2 is a left axilla-shoulder lead. E_3 is a lead made with the electrodes paired across the left arm from the inner to the outer side, 2 inches from the shoulder. E_4: Electrodes paired across the left arm, halfway between the shoulder and the elbow. E_5 is a right axilla-shoulder lead. E_6: Lead across right arm, 2 inches below the shoulder. E_7: Lead across the right arm, halfway between the shoulder and elbow. Note that the differences in potential across the left upper arm are greater than those on the right side and are comparable to those recorded in the axilla-shoulder leads. In one case of hypertension and left ventricular hypertrophy, recognizable deflections were obtained in a lead made across the left forearm.

heart is far enough from the arms to function as an electrical point in relation to them, neither shoulder electrocardiogram should be of any size, for in each shoulder lead both electrodes are on one side of the heart and are situated more or less on a line extending radially from it. Einthoven's concept does not account for the large size of the ventricular deflections in the left shoulder electrocardiogram, which are sometimes as large as those in Lead I, nor does it explain the resemblance of the left shoulder electrocardiogram to Lead I, which is striking in most subjects except for a few with anterior infarction, ventricular hypertrophy, bundle branch block, or vertically placed hearts. Finally, although the ventricular potentials in the right shoulder region behave in accordance with the Einthoven hypothesis, except in the case of bundle branch block and ventricular hypertrophy, the auricular potentials do not, for they are larger than would be expected.

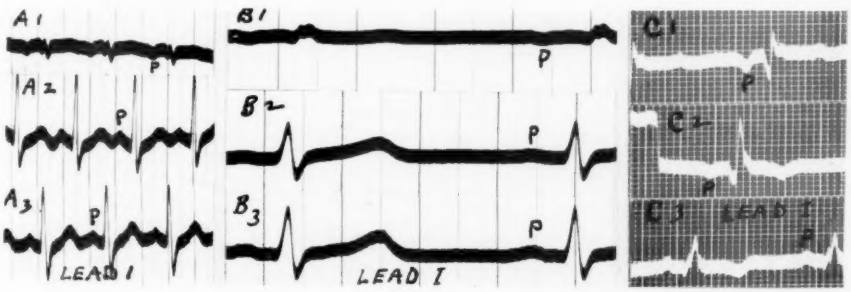

Fig. 5.—Examples of types of auricular deflections in leads made across the attachments of the arms. *A*, Patient with posterior type of infarction. A_1: Right shoulder-axilla lead. A_2: Left axilla-shoulder lead. A_3: Lead I. Although, in comparison with Lead I, the P wave in the lead across the root of the right arm is much less reduced in size than the QRS complex, it is smaller than the P wave in a lead on the left side. Had the polarity been the same on the right as on the left, the P wave would have been upright (Film speed, 25 mm. per second). *B*, Normal subject. B_1 and B_2 were made in the same way as A_1 and A_2, respectively. The P wave in the leads from the right and left sides are about equal in size, in spite of the disparity in the ventricular deflections (Film speed, 75 mm. per second). *C*, Patient with hypertension and anterior type of infarction. C_1: Right axilla-shoulder lead. C_2: Left axilla-shoulder lead. C_3: Lead I. In this case the P wave in the lead from the right side is larger than in that from the left. The QRS complex in the right-sided lead is larger than usual as is often the case in hypertension.

We had reason to hope that further experimentation might lead to an explanation of the correlation we have observed between Leads I and CF_5, so we took tracings with electrodes in various other positions. First, we made an attempt to "fractionate" Lead I. One lead was taken from the right forearm (right arm electrode) to the suprasternal notch (left arm electrode), and a second from the suprasternal notch (right arm electrode) to the left forearm (left arm electrode). The former gave a very small deflection, whereas the latter gave a much larger one which greatly resembled Lead I (Fig. 6*A*). Second, in order to obtain further information concerning the correlation between Lead I and tracings from the C_5 position, leads from the suprasternal notch (right arm electrode) to the left supraclavicular space, left shoulder, left arm, and left axilla were compared with a lead from the suprasternal notch to

the C_5 position (Fig. 6*C*). These leads were quite similar; the deflections grew larger as the left arm electrode approached the C_5 position.* Moreover, all resembled Lead I. Third, it was found that a lead from

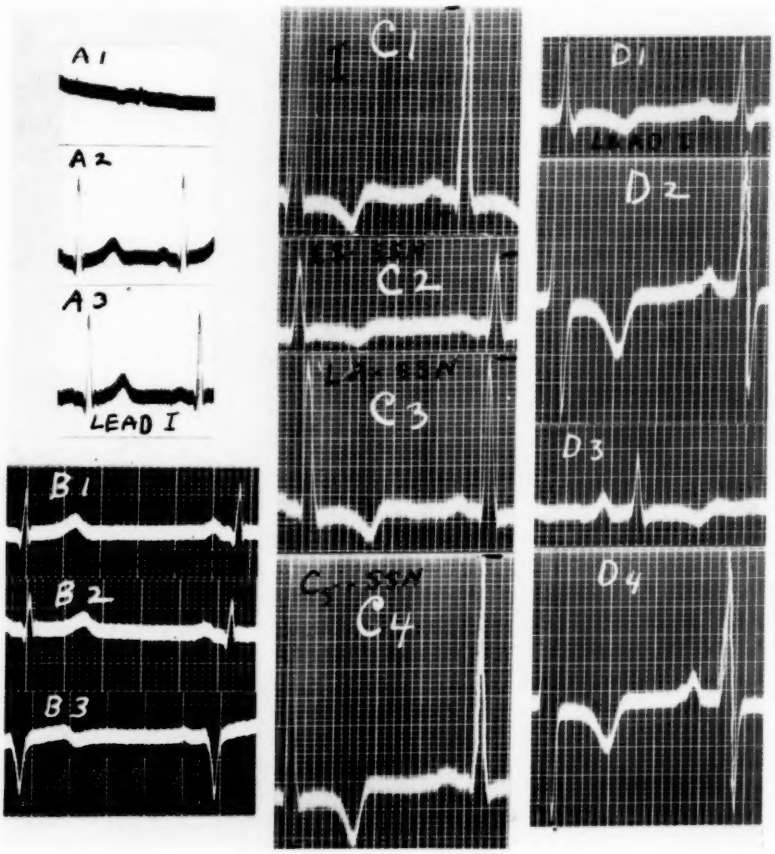

Fig. 6.—*A*, Normal subject. A_1 is a lead from the suprasternal notch to the right arm. A_2: From the left arm to the suprasternal notch. A_3 is Lead I. Note the small ventricular deflections in the lead from the right side, the large deflections in that from the left side, and the resemblance of the latter to Lead I. The P waves in the lead from the right side are reduced comparatively much less than the QRS complexes. *B*, Patient with anterior type of infarction. B_1 is Lead I. B_2: A lead from the left arm to the suprasternal notch. B_3 is CR_3. Note that the ventricular deflections in the lead from the left arm to the suprasternal notch, as well as in Lead I, bear no resemblance to CR_3. *C*, Patient with hypertension. C_1 is Lead I. C_2, C_3, and C_4 are leads made from the top of the left shoulder, the left arm, and the C_5 position, respectively, to the suprasternal notch. Note the similarity of the ventricular complexes in all of these leads. *D*, Patient with aortic insufficiency and left ventricular hypertrophy. D_1 is Lead I. D_2 is CR_5. D_3 is a lead from the left arm to the suprasternal notch. D_4: A lead from the C_5 position to the suprasternal notch. D_1 and D_3, as well as D_2 and D_4, are practically identical. The leads which include the left arm (D_1 and D_3) resemble those which include the C_5 position (D_2 and D_4), except for the comparatively larger S waves in the tracings from the C_5 position.

the suprasternal notch to the left shoulder did not reflect an abnormality which was present in a lead from the suprasternal notch to the C_5 posi-

*The correlation between leads from the suprasternal notch to the left arm and to the C_5 position is as close as that between Leads I and CR_5 (Fig. 6*D*).

tion, provided that this abnormality was absent in a lead from the suprasternal notch to the C_5 position (Fig. 6*B*).

These observations suggest that (1) some one and the same part of the ventricular muscle influences predominantly the changes in potential in the left shoulder and in the C_5 position and does not influence materially those in the right arm, (2) the auricles influence the potential change in both arms to about the same degree, and (3) the part of the ventricular muscle whose electrical activity is reflected at the C_3 position has no significant effect upon the potential changes in either arm (slight effects which it may have will be discussed below).

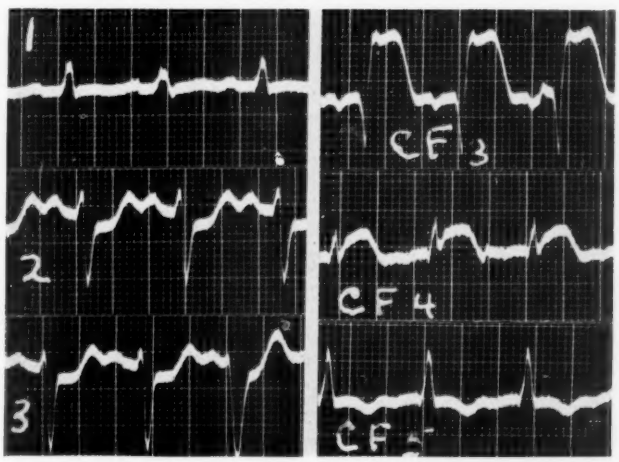

Fig. 7.—This electrocardiogram was obtained from a woman, 68 years old, five days after the onset of a succession of attacks of severe epigastric pain. At the time the tracing was made she was critically ill; death occurred a few hours later. Note the marked RS-T segment deflection in CF_3, and its absence in Leads I and CF_5. At necropsy, a fresh infarct, infiltrated with blood, was found; it involved the anterior third of the interventricular septum and extended to the anterior surface of the heart. On the surface the lesion was approximately 1 cm. wide and 4.5 cm. long; its long diameter paralleled the anterior part of the interventricular groove. Microscopic examination showed that the lesion did not seem to have extended into the anterior wall of either ventricle much beyond the limits described above for the grossly visible infarction. The anterior descending branch of the left coronary artery was completely obstructed 1 cm. beyond its origin. An additional finding was a small healed infarct at the extreme apex.

We do not possess adequate data, which should be based on careful electrocardiographic study and subsequent necropsy localization of the lesion, to state with certainty where these two portions of the ventricular muscle are situated. Such information as we do possess would suggest that, when infarction is reflected in CR_3 and not in chest leads made to the left of the C_3 position, the lesion is likely to lie in or near the anterior part of the interventricular septum (Fig. 7). On the other hand, when the lesion is reflected best in the C_5 position and in Lead I, it is likely to be located farther to the left. It may be found on further observation that the part of the ventricular muscle which affects the left arm and the C_5 position is the anterolateral portion of the left ventricle; whereas the part which affects the C_3 position and not the C_5 position

or the arms is situated close to the anterior portion of the interventricular groove. This would not be unexpected if one considered the relative positions of C_3 and C_5 on the chest wall.

One other observation might be mentioned in this connection. In cases of healed posterior infarction, when Leads I and CR_5 are normal, a lead from the left axilla to the left shoulder has a normal contour and tends to resemble Leads I and CR_5, although the deflections are smaller (Fig. 8). Thus, the electrical activity of the posterior wall of the left ventricle is probably not reflected to any extent in the left shoulder region or in the C_5 position.

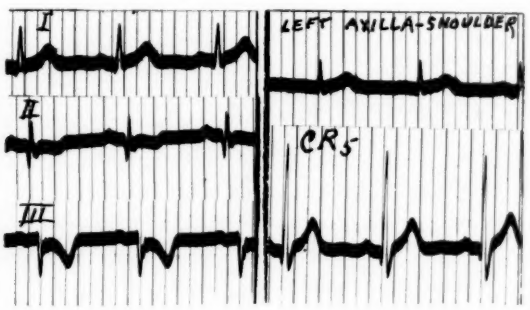

Fig. 8.—Electrocardiogram of patient with healed infarction involving the posterior wall of the left ventricle. Note the resemblance of the lead made with electrodes placed in the left axilla and on the tip of the left acromial process to Leads I and CR_5. The leads from the left shoulder region in cases of posterior infarction are likely to resemble those obtained from normal subjects.

These observations suggest that the ventricular complex of Lead I is not formed in accordance with Einthoven's conception. Rather, it seems as if its form is determined largely by the electrical activity of the left arm. This extremity seems to function as a poor sort of chest lead and to be dominated by a part of the ventricular muscle. It appears that a certain portion of the left ventricle is too close (electrically) to the root of the left arm (except in persons with long chests and vertically placed hearts) to allow the heart to function as Einthoven conceived that it would (i.e., as an electrical point) with regard to this extremity.

It is our belief that the occasional cases in which there is no correlation between Leads I and CR_5 (except for some patients with bundle branch block, vertical hearts, and anterior infarction) can be accounted for in two ways: (1) there are individual variations in the size of the heart and conformation of the chest, so that comparable areas of the heart's electrical field are not tapped from the C_5 position in each subject, and (2) certain areas adjacent to that part of the ventricular muscle which is tapped at the C_5 position probably influence the potential in the left arm to some extent.

We are aware that small deflections in the right shoulder leads, as we have taken them, do not necessarily mean that potential changes in the right shoulder are insignificant. This is the type of electrical ac-

tivity that one would expect to find if Einthoven's assumption that the heart functions as an electrical point were correct. It may be that the right arm is usually far enough away from the ventricles to satisfy this assumption. There is little doubt that the right arm plays some part in the formation of Lead I. In so far as the P wave is concerned, it is just as important as the left arm. Occasionally in cases of left ventricular hypertrophy, and usually in cases of bundle branch block, the right arm plays an important role in the formation of the ventricular complex of Lead I. Certain observations made with a two-beam galvanometer* (to be reported later) suggest that the small Q_1 in normal subjects is often derived from the right side. Moreover, other ventricular deflections may be modified by the effect of the right arm. However, as a rule, the influence of the right arm on Lead I is not great enough to blur the resemblance of the main QRS and T deflections in Lead I to those obtained from the left shoulder region.

Although the right arm may play a greater part in the formation of Lead I than is shown by our leads from the right shoulder region, this would not invalidate the tentative conclusions we have drawn from our experiments. The similarity of contour between Lead I, tracings obtained from the C_5 position, and leads from any two points along a line from the suprasternal notch leftward to the arm and thence downward to the C_5 position is such that we have been unable to account for it by any explanation except the one we have proposed.

We do not mean to imply from the above observations that the taking of limb lead electrocardiograms is not as useful a procedure as it ever was. However, unless or until evidence can be produced to support the assumptions, now under question, which Einthoven had to make to construct the equilateral triangle hypothesis, such procedures as vector analysis and attempts to measure the potential changes of a single area by Wilson's method appear to be of dubious value. We should regard limb leads as empirical; they are not yet subject to the mathematical magic of the equilateral triangle.

From the standpoint of practical clinical electrocardiography, it must be remembered that the anterior infarcts which do not produce abnormalities in Lead I are more likely to cause abnormalities in leads from the C_3 position than from C_5. Therefore, if only one chest lead is to be taken (a procedure which seems unwise at the moment), the precordial electrode should be placed medial to the apex impulse rather than lateral to it; there are a few patients who will show a Q-wave, an RS-T segment deviation, or a T-wave inversion in CF_3, and not in other leads. However, it must not be forgotten that leads from the C_3 position will occasionally show a Q wave in normal controls, and we suspect that T-wave inversion in this lead is occasionally of no pathologic significance. Hence, the abnormalities which appear in this lead must be interpreted with circumspection.

*Loaned through the courtesy of the Sanborn Instrument Company.

SUMMARY

1. The ventricular complexes of Lead I and of chest leads from the C_5 position resemble one another, both when they are normal and when they are abnormal, except for the fact that those of Lead I are usually smaller. Lead CR_5 shows a closer correlation with Lead I than does Lead CF_5. There is no correlation between Lead I and chest leads from the C_3 position. Abnormalities in the contour of tracings made from the C_4 position tend to have a counterpart in Lead I only when they are also recordable from the C_5 position.

2. When electrocardiograms are taken from each shoulder region, with the electrodes paired across the root of the arm, the ventricular deflections from the right side are, as a rule, very small, whereas those from the left are of much greater amplitude, with a few exceptions as noted in the text.

3. Ventricular complexes in leads taken on the left side of the body to the suprasternal notch from the arm and from the C_5 position, and to the top of the shoulder from the axilla (across the root of the arm) show a remarkable correlation with each other, with Lead I, and with CR_5. Leads taken from comparable positions on the right side show no analogous correlations.

4. When the relative size of the auricular complexes from the two shoulder regions is compared with that of the ventricular complexes, a definite difference is noted. The auricular complexes, instead of being larger on the left, are, on the average, of approximately equal size.

5. The foregoing observations suggest that changes in potential in the region of the left arm exert a predominating influence in the formation of the ventricular complex of Lead I, and that these potential variations, in turn, are largely dominated by those arising from that portion of the ventricular muscle which governs the contour of the ventricular complex in the C_5 position.

6. We are unable to account for our observations on the basis of the Einthoven equilateral triangle hypothesis. According to this concept, the extremities are far enough from the heart to permit it to function, in its relation to them, as an electrical point. This may be true of the right arm, for in the majority of cases there is little difference in the potential of adjacent areas in the vicinity of the right shoulder. However, the relatively large differences in the potential of adjacent areas in the vicinity of the left shoulder suggest that the left arm is too close to the heart, electrically, or at least to a portion of the left ventricle, to allow the heart to behave in relation to this extremity as Einthoven conceived that it would. Thus, the left arm must be regarded as a rather inferior chest lead position.

7. The fact that auricular deflections in right shoulder electrocardiograms are proportionately larger than ventricular deflections suggests

that, although the ventricles may be far enough from the right arm to function as an electrical point with regard to it, this is not necessarily true of the auricles.

8. Our observations do not in any way impair the usefulness of limb lead electrocardiography as an empirical procedure. However, it would seem advisable, at least for the present, to regard with a certain amount of skepticism the time-honored and elaborate, theoretical, electrocardiographic superstructure which has been erected upon Einthoven's assumptions, since there is now reason to doubt the complete validity of the two most important ones, namely, (1) that the body acts as a homogeneous fluid conductor, and (2) that the heart functions as an electrical point with regard to each of the three extremities.

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DISCUSSION

Dr. Louis N. Katz, Chicago.—Dr. Wolferth is to be congratulated for having joined those who are discarding the Einthoven triangle concept of vector analysis for general use and for having gone back to the older theory that Waller projected many years ago, when he recorded the human electrocardiogram for the first time.

A theory is valuable only insofar as it helps to advance knowledge. In the early days, the Einthoven triangle concept was useful. The facts that Dr. Wolferth presented show some of the fallacies of this concept; others we have pointed out in our work. The return to the old "field theory" offers many possibilities of obtaining new information without the handicap imposed by the theoretical, mathematical, and not too accurate concept of the equilateral triangle.

THE USE OF THE CATHODE RAY FOR RECORDING HEART SOUNDS AND VIBRATIONS

III. Total Cardiac Vibrations in One Hundred Normal Subjects

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IN RECENT years phonocardiography has acquired a definite place in the diagnosis of heart disease. The registration of the heart sounds for clinical purposes was greatly facilitated by the introduction of electrical stethographs, whose convenience of use and superior accuracy in recording are signally superior to the older methods.[1] However, these stethographs have usually been constructed in such a way as to emphasize murmurs and other adventitious sounds. Such records may be of distinct value in studying certain adventitious sounds, especially as regards their relation to the cardiac cycle. Little, if any, attention has been paid to the general character of all of the vibrations produced by the heartbeat, the audible frequencies of which make up the heart sounds. As was pointed out in a previous communication,[1] certain fundamental changes in the heart tones may occur in various kinds and stages of heart disease; it would seem advantageous to record all of the vibrations set up by the heartbeat, both audible and inaudible, so that these fundamental changes, which may be obvious to the ear, can be recorded and studied.

The object of this communication is to present a composite study of tracings of total cardiac vibrations which were obtained from 100 normal young adults.

PROCEDURE

The subjects were medical students and nurses, whose ages ranged from 20 to 35 years. All of them had previously had complete physical examinations, including roentgenograms of the chest, and were presumed to be in good health. The instrument used for recording the heart vibrations was the vibrocardiograph. A detailed description of the device has been presented.[1] In most cases the vibrocardiographic tracings were recorded simultaneously with Lead II of the electrocardiogram, and the records were synchronized by flashing lamps which played on the two records simultaneously.[1] During the procedure the subject lay supine for ten to fifteen minutes, until stability of the heart rate was assured. The blood pressure, which was recorded during the period of rest, was within normal range in each case. Tracings were obtained from the aortic, tricuspid, mitral, and pulmonic areas. In some cases the pickup unit was placed at other locations on the anterior chest wall, in an effort to discover whether there were variations in wave forms and intensities outside of the usual auscultation areas.

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DESCRIPTION OF THE RECORDS

The dominant vibration groups in normal vibrocardiograms are those incident to the onset of systole (embodying the audible frequencies of the first heart sounds) and those incident to closure of the semilunar valves. In analyzing the first (systolic) vibration complex, a group of small preliminary waves (one to three in number) could usually be seen in records from all of the four auscultation areas. They were interposed between the P wave and the crest of the R wave, and immediately preceded the large principal vibrations of which the first sound is a part. The time of occurrence of the preliminary waves would seem to be just prior to the rise of intraventricular pressure at the onset of systole; they correspond in time to the "preliminary vibrations" noted by McKee.[2] It is possible that these ripples are caused by the forcible ejection of blood from the auricles into the ventricles during auricular systole. It is likewise possible that they may be induced by movements in the ventricular muscle when it is further distended by the force of auricular systole.

The main deflections follow the preliminary waves and consist of spikes of higher amplitude and frequency. These main deflections begin immediately after the peak of R and then taper into lower-frequency, lower-amplitude waves which finally disappear at, or just after, midsystole. Since the principal deflections include the audible components which comprise the first heart sound, the sound itself, therefore, falls on the descending limb of the R wave. The total duration of the first vibration complex, including the preliminary waves and the main deflections, with the audible frequencies, ranges from 0.19 to 0.29 second and averages 0.22 second when the heart rate ranges from 70 to 85 per minute. The duration of the main wave complex (i.e., deflections following the peak of R, including the audible portions) is from 0.08 to 0.19 second, and averages 0.11 second in the entire series of cases. The wide variation in the duration of the first vibration complex possibly depends on several factors, such as rapidity of rise of interventricular tension, thickness of the auriculoventricular valves, and the blood pressure level. It is interesting that, although subtle differences in the heart sounds may be detected in normal persons by auscultation, there may be striking variations in the shape of the waves of the first sound complexes among normal persons, as recorded by the cathode-ray oscillograph. Such changes appear to be caused by alterations in the lower-frequency components, without much visible modification in the sharp waves which produce the sound. It is likewise of interest that the shapes of successive waves from a given subject are remarkably constant, so long as the basal state remains undisturbed. The significance of the low-frequency components and other variations in the curves will be discussed later.

It is generally thought that the second heart sound is caused by the closure of the pulmonic and aortic valves. In the records obtained with the vibrocardiograph, or by ordinary phonocardiography, the second sound is sharper in profile and shorter in duration than the first sound complex. In this series, the second sound complex, both at the pulmonic and aortic areas, consisted of one to three sharp waves which ranged from 0.04 to 0.09 second in duration (averaging 0.06 sec.), with frequencies of approximately 80 to 90 d.v. per second. This is in agreement with the results obtained by most workers. The second sound complex falls on the descending limb of the T wave of the electrocardiogram. The amplitude of the deflections (sound intensity) is probably directly related to the level of the aortic and pulmonic pressure, as noted by Wiggers and Dean.[3]

General analysis of the duration of the vibrocardiographic curves with relation to the duration of systole, diastole, and the first and second sound complexes showed variable results. It is known that acceleration of the heart rate shortens diastole, and, occasionally, systole. A rise in blood pressure caused an increase in the duration of the first sound complex, apparently by prolonging that part which followed the peak of R. Age had some effect on the duration of the first sound. As a rule, the younger the subject, the shorter were the systolic vibration complexes, and, the older the subject, the longer were the systolic vibrations. The duration of the first vibration complex was generally shorter in female than in male subjects. The ratio of the duration of the first and second vibration complexes was roughly two to one, although, when the heart rate was fast, the two sounds frequently tended to be of the same duration. The point of contact also affected the ventricular complex; generally the vibrations at the aortic and tricuspid areas were more prolonged than at the pulmonic and mitral areas.

It is said that a third heart sound may occasionally be audible in early diastole, but none of our 100 subjects had a diastolic third heart sound. However, in 7 per cent of the tracings, there was, following the second sound complex, a large wave at the time when the third heart sound might be expected to occur (i.e., approximately 0.1 sec. after the second sound). The deflection was of too low a frequency to be heard. There is a general feeling that rapid ventricular filling in early diastole, producing sudden distension of the ventricular walls, creates vibrations which sometimes may be heard.[4] Hirsch and Gubner,[5] who studied cardiac movement by means of roentgenkymography, found that a sharp break occurs early in the diastolic wave from normal hearts. They interpreted this as representing sudden ventricular distension caused by rapid filling of the ventricular cavities. It would thus seem possible that sudden ventricular distension in early diastole

might produce a single movement which would register as a single, low-frequency wave.

Another group of subjects (5 per cent of the series) showed low-frequency, low-amplitude waves (below acoustic level) in diastole. There were usually three waves, although occasionally only two were evident. The phenomenon occurred principally in persons who had been athletes. It is curious that the diastolic waves were usually most marked in tracings made from the tricuspid or aortic areas. Occasionally they were more conspicuous when the receiver was placed at some point along the right sternal border. They appear to be the result of myocardial motion, as will be discussed later.

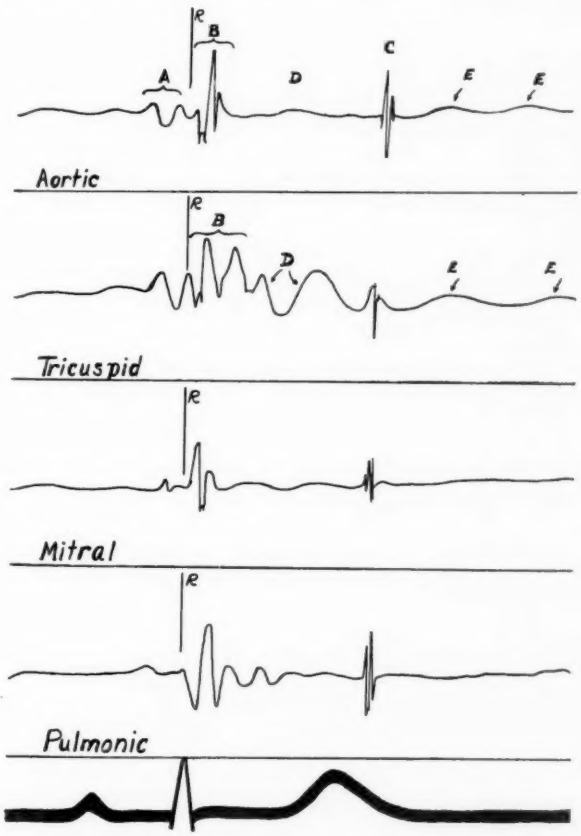

Fig. 1.—Diagrammatic sketch of typical vibrocardiographic curves in relation to Lead II of the electrocardiogram. The vertical line (*R*) represents the time of occurrence of the R wave. The preliminary waves (*A*) occur between P and R of the electrocardiogram. *B* indicates the "main deflections" at the onset of systole which embody the audible frequencies of the first heart sound. The peaked deflections (*C*) comprise the second heart sound. *D* and *E* are the low-frequency, inaudible waves which occur in systole and diastole.

In ordinary phonocardiography, murmurs and other adventitious sounds may appear particularly clear because of damping out of lower vibration frequencies and amplification of the higher; therefore,

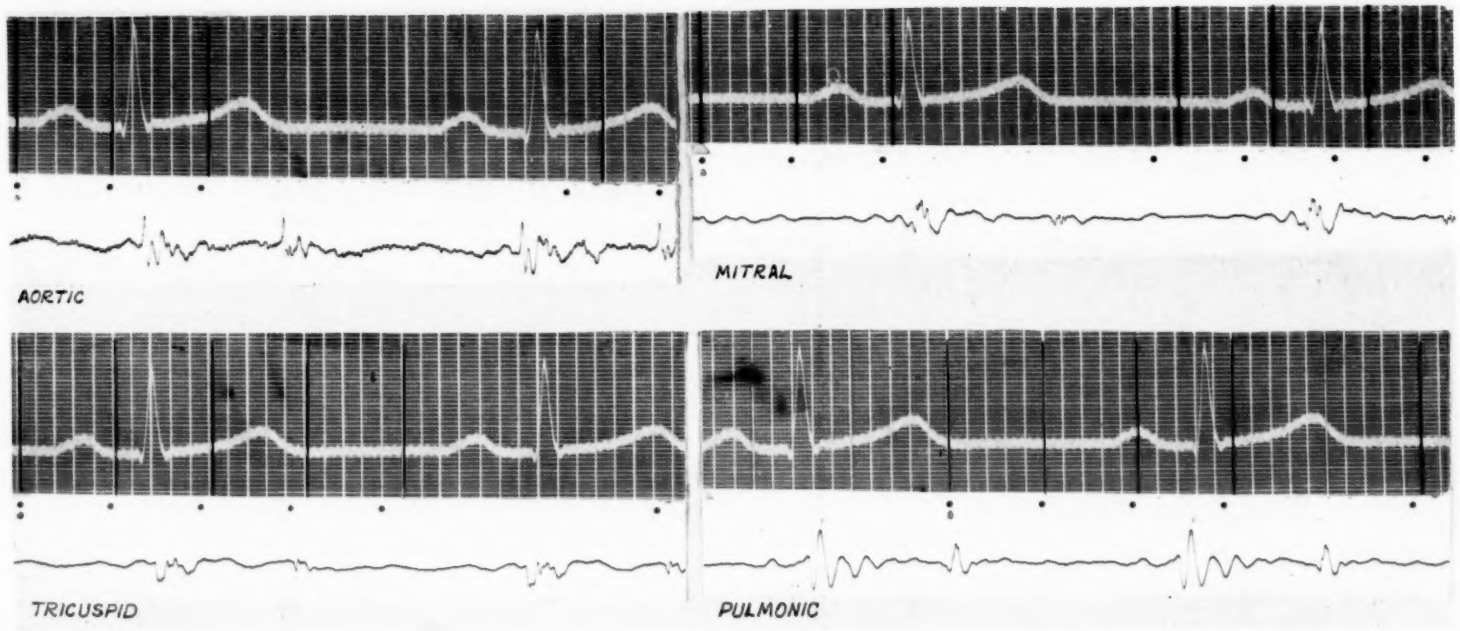

Fig. 2.—Vibrocardiogram of normal subject, synchronized with electrocardiogram (at approximately twice normal speed). The first and second sound vibration groups may be readily recognized. In each curve, low-frequency systolic undulations are seen, especially at the pulmonic area. The black dots on the vibrocardiogram and the black lines on the electrocardiogram represent intervals of 0.2 second; occasional interruptions in the lights indicate corresponding points on the records.

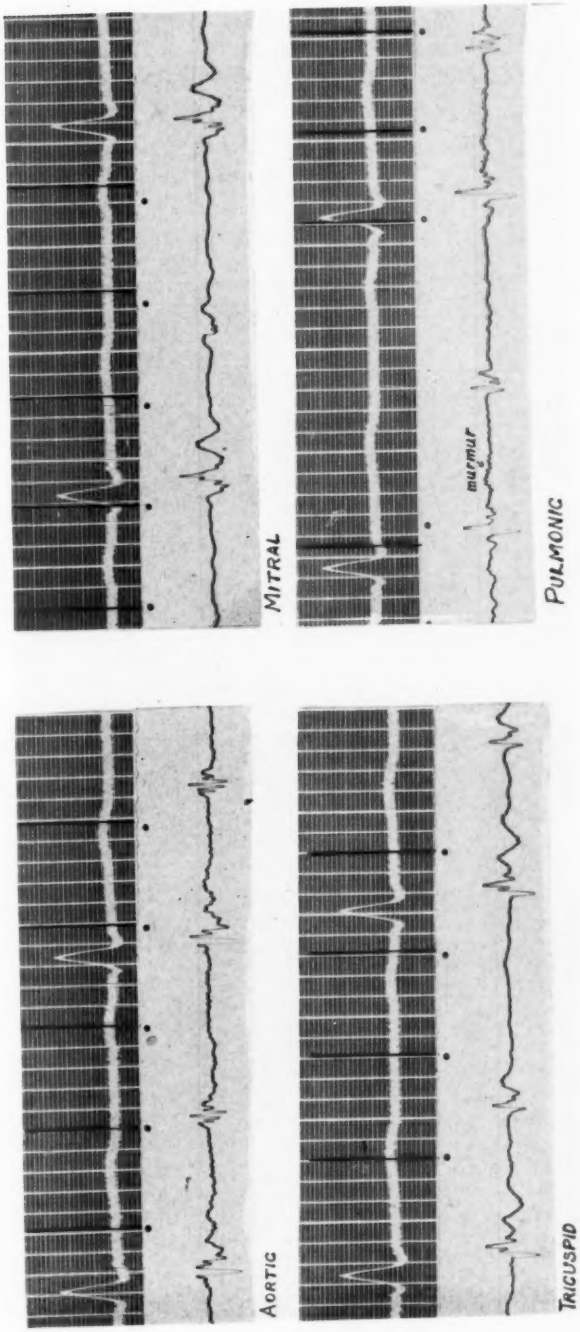

Fig. 3.—Synchronized vibrocardiogram and electrocardiogram of a normal subject. A faint, blowing, pulmonic systolic murmur was detected with the subject lying supine. Low-amplitude, high-frequency waves may be seen in the systolic interval of the record taken from the pulmonic area. As the murmur was of low intensity in comparison with the other heart sounds, it appears as diminutive waves in the tracing.

the deflections representing a murmur may be out of all proportion to the intensity at which they actually occur, as compared with the intensity of the heart sounds. Tracings obtained by this method will show that the vibrations incident to the murmur are of low amplitude if the intensity of the murmur is small in comparison with other sounds produced by the heartbeat. If, however, a murmur is loud, as in well-marked aortic stenosis, the sound may be registered as a series of tall, high-frequency, systolic waves. One frequently encounters pulmonic systolic murmurs in normal persons, especially when the subject is

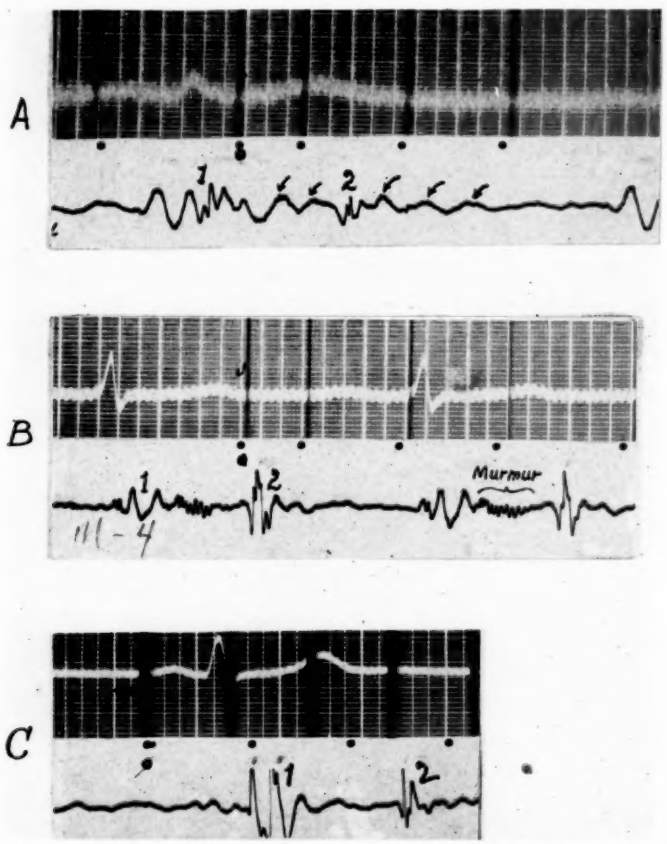

Fig. 4.—Vibrocardiographic curves, synchronized with Lead II of the electrocardiogram, picked at random from the series of cases. *A*, Curve obtained from the tricuspid area of a subject who showed low-frequency systolic and diastolic waves (marked by curved arrows). *B*, Curve obtained from the mitral area of a subject with a functional mitral systolic murmur. Note the high frequency systolic waves which represent the murmur. The intensity of the murmur is proportionate to that of the first and second sounds. *C*, Vibrocardiogram taken from the tricuspid area of a subject who had "splitting" or reduplication of the first heart sound. Note the two, tall, peaked waves, separated by a short segment; each wave has steep, audible slopes.

in the reclining position. This is best shown in Fig. 3; small, high-frequency waves are noted in the systolic intervals of the tracings obtained at the base of the heart. In this instance the murmur was faint; consequently, in the curve it is diminutive in comparison with the other waves.

An interesting occurrence in some normal hearts is splitting of the first or second sounds. In tracings recording total heart vibrations, this appears as a reduplicated or doubled series of tall deflections, with steep slopes as the audible portions (Fig. 4).

COMMENT

Curves were obtained from 100 normal subjects under as nearly uniform conditions as possible, and the tracings were generally similar. As noted before, the wave shapes may vary widely, although, to auscultation, the heart sounds may seem to differ but little. These variations in contour appear to be dependent largely on modification of the lower-frequency vibrations incident to ventricular systole. A survey of the material shows that the sharpness of the first vibration complex is not related to the duration of systole or diastole, for there may be shortened first sound vibration complexes when either systole or diastole is prolonged or shortened. However, it is recognized that the quality and intensity of the sounds may change in normal subjects, depending on the conditions under which the heart must work. Wiggers[6] found that, within certain limits, a change in the vibrations produced by the beating heart was an indication of a change in the rate of rise of intraventricular tension during the isometric phase of contraction. Thus, the speed and force with which the ventricle contracts, whether the subject is at rest or active, may determine the sharpness and intensity of the heart sounds. The heart tones may likewise be influenced by the size of the chest and the thickness of the chest wall. Obesity or a well-developed thoracic musculature may diminish the intensity of the vibrations, whereas in slender subjects the vibrations may seem particularly clear.

Of greater interest, we believe, than the recording of sound intensities and murmurs, are the low-frequency, inaudible deflections incident to the systolic and diastolic phases of ventricular contraction. The main vibrations of the first heart sound, or the tapering vibrations themselves, often embody such low-frequency waves. The cause of these systolic waves is not yet clear. Smith, Kountz, and Gilson,[7] working with hearts of dogs, noted that, when the auriculoventricular valves were immobilized, the vibrations produced by contraction of the myocardium alone were large and of low frequency, with slopes as steep as those of the audible vibrations. Such waves, as recorded from the beating dog heart, often bear a striking similarity to the low-frequency waves which are part of the first vibration complex in tracings from normal subjects. It is possible that these low-frequency waves indicate myocardial motion per se, and that they may result from additional contractile motions of the heart during systole.

Of equal interest are the low-frequency, low-amplitude diastolic waves which occur in some normal subjects, particularly in athletes.

As noted before, they are usually maximum at the aortic or tricuspid areas. In casting about for an explanation of this phenomenon, it first seemed likely that they might result from gross, pendulous motions of the heart, made possible by the mobility of the mediastinum and the resilience of the lungs. However, altering the position of the subject neither abolished nor accentuated the waves, although one might have expected a modification of the waves if a pendulous, swaying movement of the heart were a factor. It was also necessary to consider the possibility that the resonating properties of the chest might produce low-frequency waves incident to the heartbeat, but the deflections in question were found not to vary with respiration, nor to be influenced by tight strapping of the chest, which increased the resonating properties of the chest. It seems most likely, therefore, that the diastolic waves arise from motions of the myocardium itself. How such motion is produced, or why it occurs, is still a moot point. Recent work[8-10] suggests that diastolic waves may be caused by the passage of recoiling movements over the ventricular muscle, giving the appearance of a "notch-like" dilatation, rather than a smooth dilatation. If this were the case, one would expect such a phenomenon to occur universally. It is possible, however, that under some conditions they may be damped out.

SUMMARY

The usual study of heart sounds is limited to the recording of the sound vibrations only, with little attention to other vibrations produced by the beating heart. In this investigation, all of the cardiac vibrations at the usual auscultation areas in 100 normal young adults were recorded by means of a cathode-ray vibrocardiograph. The intensity and duration of the first and second sound vibration groups were studied in relation to the length of the systolic and diastolic phases of the cardiac cycle. With this method, murmurs are reproduced at the intensity with which they occur, and, if faint, may appear diminutive in comparison with the deflections which represent the heart sounds. Most interesting are the low-frequency vibrations, below the auditory level, which occur in systole and diastole and possibly indicate myocardial motion alone.

The authors wish to express their appreciation to the Burdick Corporation, whose cooperation made this work possible.

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Department of Clinical Reports

ANTE-MORTEM DIAGNOSIS OF RUPTURE OF THE INTERVENTRICULAR SEPTUM AS A RESULT OF MYOCARDIAL INFARCTION

Report of a Case

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Sager,[1] in 1934, collected from the literature seventeen cases of rupture of the interventricular septum as a result of myocardial infarction and added one of his own. Additional cases have since been reported by Gross and Schwartz,[2] Stern,[3] Stanley,[4] and Scott and Garvin.[5] In only three cases (Sager,[1] Stanley,[4] and Brunn[6]) was the diagnosis of rupture of the septum made before death. The case herewith reported brings the number of cases on record to twenty-three, and the number of correct ante-mortem diagnoses to four.

CASE REPORT

J. N. D., a white man, 47 years of age, was admitted to the medical service of the Charity Hospital of Louisiana on Nov. 20, 1939. Three weeks before, about thirty minutes after the noon meal, he had experienced a sudden, moderately severe, burning pain behind the upper part of the sternum. It radiated to the left shoulder and down the left arm and was accompanied by weakness and nausea. A physician who examined the patient shortly after the onset found nothing wrong with his heart, but told him that his blood pressure was high (''180 systolic''). The pain, which was attributed to indigestion, subsided completely within two hours, and after three days the patient was well enough to return to work. A few days later his physician again examined his heart and assured him that there was nothing wrong with it. His blood pressure at that time was 160/120.

A second attack occurred one week later, as the patient was on his way home from work. The pain at this time was confined to the left hypochondriac and epigastric regions and was of a moderately severe, burning character. It was accompanied by nausea, vomiting, weakness, and shortness of breath. Several hours after the onset the patient began to cough and to expectorate bloodstreaked sputum. An hour later his physician listened to his heart and told him that he had ''heart trouble.'' A consultant who saw him at this time said that he had ''a leak in his heart.'' He was advised to enter the hospital at once, but did not accept the advice until two weeks later. In the interim he remained in bed at home.

The patient had had semiannual physical examinations throughout the preceding five years and had felt entirely well until the onset of the present illness. During this period his systolic blood pressure had supposedly ranged between 160 and 180. No family history of heart disease could be obtained. He had had a penile lesion at the age of 27 years, for which he had been treated with injec-

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tions in the arm. On several occasions afterward he had been told that his blood Wassermann reaction was negative.

He was a rather poorly nourished patient, of asthenic habitus, who was supported by a back rest in the semirecumbent position. He was moderately dyspneic and seemed seriously ill. His temperature was 98.2° F.; his pulse rate, 82; his respiratory rate, 20 per minute; and his blood pressure, 120/100.

The pupils were circular, equal, and reacted promptly to light and in accommodation. The external jugular veins were moderately distended. There was slight dullness in the left subscapular region, and fine, moist râles were heard at the bases of both lungs posteriorly.

The cardiac apex impulse was in the sixth left intercostal space, about 9 cm. from the midsternal line. The pulsation was well localized and moderately forceful. A pronounced thrill was felt over the lower precordium, just to the left of the sternum. The first heart sound was not audible. The second sound was quite loud at the pulmonic area. A loud, rough murmur of medium pitch, which lasted throughout systole, was heard best 3 cm. to the left of the sternum in the fourth and fifth intercostal spaces and was transmitted over the entire precordium. The rhythm was normal.

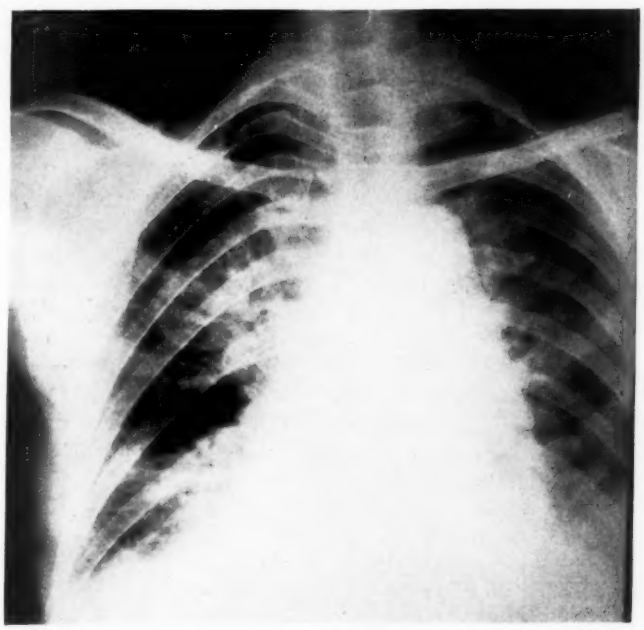

Fig. 1.—Roentgenogram of chest, showing moderate cardiac enlargement and pulmonary edema.

The edge of the liver was 4 cm. below the right costal margin and was slightly tender. There was no edema over the sacrum or of the extremities.

Urinalysis showed a trace of albumin and a few erythrocytes. The erythrocyte count was 3,500,000; the leucocyte count, 8,050. The hemoglobin was 80 per cent (Sahli). The neutrophiles numbered 66; the lymphocytes, 23; and the monocytes, 11 per cent. The blood Kline and Kolmer reactions for syphilis were negative.

A roentgenogram of the chest (Fig. 1), taken just after the patient was admitted to the hospital, showed a moderate, general enlargement of the cardiac

silhouette. The aortic knob was prominent, and there was calcification of the aorta. Dense mottling was seen throughout both bases and in the region of the hila of the lungs; this was interpreted as evidence of pulmonary edema. The left costophrenic angle was obliterated, probably by a small quantity of fluid. The first and last of several electrocardiograms which were taken during the period of hospitalization are presented in Fig. 2.

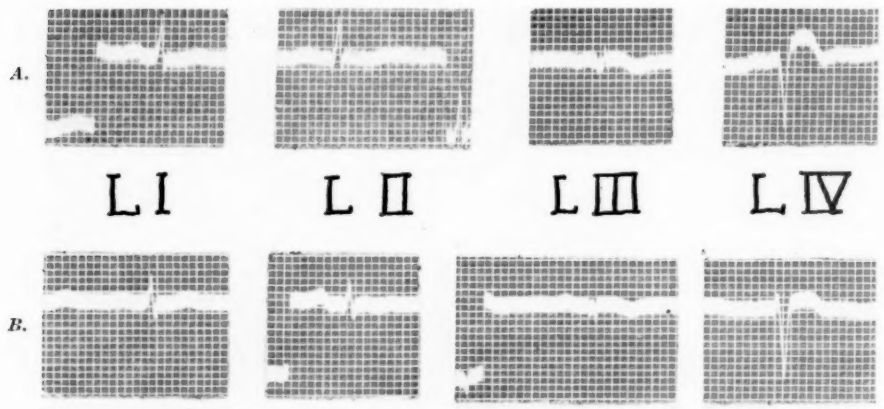

Fig. 2.—Initial and final electrocardiograms. *A*, Nov. 21, 1939. *B*, Jan. 2, 1940. Leads I, II, and III show Q_2 and broad Q_3. Slight deviation to the right of the mean electrical axis of QRS has developed in the lower curve. Lead IV F shows absence of R (upper curve) and elevation of the RS-T junction.

Two weeks after the patient was admitted to the hospital edema appeared in the lower extremities. The administration of digitalis, which had been given continuously, was discontinued at this time because of nausea and vomiting. With the appearance of the edema, the distention in the neck veins increased, the apex impulse became diffuse, and the left border of cardiac dullness extended to the left anterior axillary line. The blood pressure was 120/86. During inspiration, the border of the liver descended 8 cm. below the right costal margin.

There was a transient response to treatment with a neutral-ash, salt-poor diet, ammonium chloride, salyrgan, and restricted doses of digitalis, but congestive heart failure soon became marked. Ascites developed; edema of the chest and abdominal wall appeared; the sclerae and the skin of the head and neck became icteric (index 18); and the dullness and râles at the bases of both lungs became more marked. The precordial thrill and murmur remained unchanged throughout the illness. Death occurred eight weeks after admission to the hospital.

Ante-Mortem Diagnosis.—A diagnosis of rupture of the interventricular septum as a result of myocardial infarction was made shortly after the patient was admitted to the hospital, for the following reasons: The history and electrocardiographic changes were thought to be sufficient to establish the diagnosis of hypertensive and arteriosclerotic heart disease, with cardiac infarction. Inasmuch as left axis deviation might be expected in a case of hypertension which had lasted five years or more, the form of the patient's electrocardiogram was considered indicative of some further abnormality. The changes in Leads I, II, and III indicated injury to the diaphragmatic wall of the left ventricle and neighboring portion of the interventricular septum.[7] On the other hand, the QRS complex of Lead IV F was considered diagnostic of infarction of the anterior wall of the left ventricle near or at its apex. The upward displacement of the

RS-T junction and segment in this lead was regarded as indicative of recent injury in the anterolateral wall of the left ventricle.

Fig. 3.—Anterior view of the heart, showing aneurysmal dilatation of the ventricular apex. The descending branch of the left coronary artery has been opened.

Fig. 4.—View of the heart looking into the left ventricle toward the interventricular septum, which appears white and fibrotic throughout its lower third. Three septal perforations are seen just above the lower glass rod.

A thrill and a loud systolic murmur over the center of the precordial region are characteristic signs of a defect in the interventricular septum. The fact that these signs, according to the patient's history, had only recently appeared, to-

gether with the whole clinical picture and the electrocardiographic evidence, made it appear almost certain that rupture of the septum, near the apex, had occurred. The development of high-grade, right-sided heart failure after the patient entered the hospital, and the small but definite S_4 lent still further support to the diagnosis of rupture of the interventricular septum.

Autopsy.—Post-mortem examination revealed a moderately enlarged heart and an aneurysmal dilatation of the apex of the left ventricle (Fig. 3). The heart weighed 485 Gm. The wall of the basal region of the left ventricle measured 14 mm. in thickness, but the wall of the aneurysmal sac at the apical region measured only 2 mm. The right ventricular wall was 10 mm. in thickness in the basal region, and 7 mm. in the apical region. The mitral valve admitted two fingers with ease; and the tricuspid valve, the tips of four fingers. The pulmonary conus was slightly dilated. The first portion of the aorta was of normal size; it exhibited moderately severe atherosclerosis. The basal region of the interventricular septum bulged moderately into the chamber of the left ventricle and thus formed part of the dilated infundibulum of the right ventricle. The apical third of the interventricular septum formed the right lateral wall of the aneurysmal sac at the apex of the left ventricle and protruded into the apical region of the right chamber for a distance of 2.75 cm. At the apex of this protrusion there were three irregular openings (Fig. 4) which connected the two chambers. The total area of the openings was approximately 2.5 sq. cm.

The entire inner surface of the aneurysmal sac was white and densely fibrotic, as might be expected ten to eleven weeks after infarction. The aneurysm, in addition to involving the apical third of the interventricular septum, extended upward from the apex on the anterior left ventricular wall for a distance of 4.5 cm. and upward from the apex on the posterior left ventricular wall for a distance of 1.5 cm.

Arteriosclerosis had caused marked narrowing of the first part of the right coronary artery and moderate narrowing of the left coronary artery. No area of total occlusion was found.

COMMENT

The diagnosis of rupture of the interventricular septum as a result of cardiac infarction, although it has been made in only four of the twenty-three reported cases, including the case herewith reported, should in most instances be quite simple. It depends chiefly upon keeping in mind the possibility of rupture when a patient presents the clinical manifestations of cardiac infarction and the precordial signs of a septal defect. If it can be established by the history or by observation that the latter appeared after the onset of the infarction, the diagnosis is almost certain. If the patient survives the acute stage, the appearance of high-grade, right-sided congestive heart failure supports the diagnosis of septal rupture and helps to exclude the possibility of a torn papillary muscle. The development, after the acute stage, of deviation to the right of the mean electrical axis of QRS offers a measure of confirmation to the diagnosis of septal rupture.

SUMMARY

1. A case of rupture of the interventricular septum as a result of cardiac infarction is added to the twenty-two others already on record in the literature.

2. A correct ante-mortem diagnosis was made in this case, bringing to four the number of cases in which the condition was recognized before death.

3. The considerations which led to the ante-mortem diagnosis are outlined, and it is pointed out that, although the condition is rare, it should be diagnosed if the physician bears the possibility in mind when he is confronted with a patient who presents the clinical manifestations of cardiac infarction and the precordial signs of a septal defect.

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ACUTE RHEUMATIC HEART DISEASE IN THE AGED

Report of a Case With Unusual Clinical Manifestations

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INTRODUCTION

THE acute rheumatic state is generally regarded as a childhood disease, usually associated with cardiac involvement. Leonard,[1] who studied a large series of cases (500), reported that the highest incidence of initial attacks occurred between the ages of 5 and 11 years, and that 71 per cent of the patients developed rheumatic heart disease and suffered most of their recurrences before puberty. Juster,[2] in an exhaustive study of fifty-nine patients with chronic rheumatic heart disease between the ages of 15 and 44 years, demonstrated that reactivation of the rheumatic carditis was a usual and common occurrence, but Rothschild[3] and his collaborators, in a series of 161 cases of chronic rheumatic heart disease, noted activity only twice in the sixth decade and but once in the seventh decade. In this latter case, that of a woman of 62 years, there was evidence of old coronary occlusion and recent bronchopneumonia. Thus, active rheumatic carditis is rare in the later decades of life, yet in the following case there was a widespread, uncomplicated, active, rheumatic myocardial inflammatory process in a woman of 61 years which caused her death after extraordinarily confusing clinical manifestations.

CASE REPORT

M. L., a white widow, 61 years old, had been in excellent health as long as she could remember. She was 5 feet 5 inches in height and weighed 150 pounds. At no time did she recall having any symptoms of the rheumatic state, nor had any cardiac lesion ever been discovered. Only once did she require medical service, and this was during her only pregnancy (which was normal), when she was 20 years old. The child had the usual diseases of childhood, but nothing indicative of rheumatism, and is now a healthy, 40-year-old man. The patient worked in a shirt factory for many years until Feb. 13, 1939, when she developed an attack of tonsillitis, associated with high fever, a feeling of exhaustion, and severe bodily aches. The following morning a severe earache began, and, within twelve hours, there was a discharge from the left ear, but the pain persisted. An otolaryngologist discovered rupture of the ear drum and advised irrigations of the external auditory canal. Two days after the onset her temperature had returned to normal and her condition was greatly improved. The discharge from the ear gradually subsided, and ended on the tenth day, when the patient returned to work, apparently well.

One week later, vague pains in the wrists were experienced for the first time; these lasted for a few days. There was no swelling of these or any other joints. On March 16 slight dyspnea on exertion developed, but grew no worse until 4 A.M., March 19, when she was awakened by a severe attack of dyspnea, accompanied by

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cyanosis and pulmonary edema. Relief immediately followed the administration of 10 c.c. of aminophyllin intravenously, together with a hypodermic of ¼ grain of morphine sulfate. Thirty-six hours after this attack of nocturnal dyspnea there were a fever of 103° F. and a very painful polyarthritis, involving chiefly the wrists and shoulder joints.

Upon admission to the City of Kingston Hospital on March 20, 1939, the temperature was 103.4° F., the pulse rate was 110, with numerous premature systoles, and the blood pressure was 138/80 mm. Hg. Both wrists were swollen, red, and painful, and there were pain and limitation of motion of the shoulder joints. A few scattered petechiae were present in the skin over the abdomen and left forearm. The heart was not enlarged to percussion, but there was a soft, apical, systolic murmur of moderate intensity which was not transmitted, and the pulmonic second sound was accentuated. The liver extended 3 cm. below the right costal margin and was slightly tender, but no pulsation could be felt. Râles were heard at the bases of the lungs, and there was moderate edema of the lower extremities. Dyspnea and orthopnea were marked, but the cyanosis had disappeared. There were no other significant physical signs. The tonsils were small and not inflamed, and the eye grounds were not remarkable. The erythrocytes numbered 3,300,000 per cu. mm., and the hemoglobin was estimated as 10 Gm. per 100 c.c. A rather marked leucocytosis was present (23,650, 88.5 per cent of which were polymorphonuclears). There was a pronounced albuminuria, and the urinary sediment contained a few erythrocytes, some granular and hyaline casts, and large numbers of leucocytes. There was no nitrogen retention in the blood except for a uric acid value of 5.0 mm. per cent. The blood chloride and cholesterol content was within normal limits, and a blood culture yielded no growth after two days' incubation. Roentgenologic studies of the paranasal sinuses, mastoids, and lungs showed nothing abnormal. The cardiac shadow was not enlarged, nor was there any accentuation of the pulmonary conus. Electrocardiograms confirmed the clinical impression that there were many premature ventricular systoles, but otherwise showed nothing of importance. There was no axis deviation, and the P-R interval was not prolonged. At this time a tentative diagnosis of subacute bacterial endocarditis was made, in spite of the fact that organisms had not been isolated from the blood and no history or physical evidence of previous cardiac disease could be obtained.

The course of the disease, which extended over a period of seven weeks, was not characteristic of subacute bacterial endocarditis, but no other plausible explanation for the clinical manifestations in a patient 61 years of age came to mind. The possibility of generalized lupus erythematosus was considered, but because of the continued absence of any skin manifestations and the wide dissimilarity between the clinical signs and those of the Libman-Sacks syndrome, it was felt that this could be ruled out.

The temperature was of the undulating type; it rose at two-week intervals to 103° F. and then gradually fell to slightly above the normal level, but at no time returned to normal. Large doses of neoprontosil had no effect on the hyperpyrexia. The leucocyte count ranged from 14,500 to 23,000 per cu. mm. Albumin, moderate numbers of erythrocytes, and leucocytes persisted in the urine. Four blood cultures, taken at regular intervals, remained sterile after nine days' incubation. The anemia did not progress.

No increase in the size of the heart was ever detected; the systolic murmur was inconstant, but never increased in intensity or changed in quality. The pulmonic second sound became somewhat louder, and there were long intervals when no extrasystoles could be detected. Several subsequent electrocardiograms were the same as that taken upon admission; at no time did they reveal evidence of myocardial disease. The peripheral edema and the dyspnea responded slightly, if at all, to adequate

digitalization, but great improvement followed the administration of aminophyllin parenterally.

After two weeks' rest in the hospital the arthritic manifestations had practically subsided, and then there was a rather sudden exacerbation of the symptoms, involving the same joints.

The most striking feature of her illness was the seven attacks, all of which were essentially the same, of sudden dyspnea, followed rapidly by cyanosis and signs of pulmonary edema. The first six of these attacks responded very well to aminophyllin, given intravenously, and morphine, given subcutaneously, but the seventh was fatal.

POST-MORTEM EXAMINATION

The body was fairly well nourished. There was no edema. Faded petechiae were seen on the chest and arms, but not more than six or eight, in all, could be recognized. The liver was moderately enlarged and markedly congested, and, upon section, showed very prominent lobulations like those found in chronic passive congestion. The spleen was not remarkable; its pulp was firm and brownish red, in no way resembling chronic splenic tumor. No petechiae were found in the kidneys, intestines, or other abdominal viscera. The heart was slightly enlarged; it weighed 350 Gm. and was bathed by an increased quantity of clear, straw-colored fluid. There was no exudate on the epicardium, but it presented a dull, grayish appearance which, upon close inspection, was found to be caused by minute, discrete, grayish areas under the serosal surface. The cardiac hypertrophy was limited entirely to the slightly dilated left ventricle. The mitral valve was moderately thickened, and its chordae tendineae were somewhat enlarged and shortened. Along the line of closure many minute, almost transparent vegetations appeared. These vegetations were precisely like those which occur in acute rheumatic heart disease. It was very striking how the small blood vessels in the myocardium stood out as whitish lines. When these were cut across, they appeared as whitish oval and circular nodules. The aortic cusps were slightly stiffened, and, along the line of closure, there were the same minute, translucent vegetations. The tricuspid valve, except for slight thickening, showed no significant alteration. The coronary vessels were patent down to the smallest visible division, but, in places, the wall was concentrically thickened at the expense of the lumen, and much of this thickening was intimal. There were no scars in the myocardium which in any way suggested that vascular occlusion had occurred. The aorta was altered by thick intimal patches around the orifices of the coronary arteries, but otherwise showed nothing. Each pleural sac contained approximately 500 c.c. of clear fluid, and the lungs were the seat of rather marked edema. They were pale in color and showed no evidence of long standing passive congestion; there was no gross evidence of consolidation.

Histologic studies revealed the largest and greatest number of Aschoff bodies in the myocardium that we have ever seen. The inflammatory process had actually destroyed large areas of muscle fibers and extended to the endocardium and epicardium. All of the muscle fibers were swollen and stained poorly, and many were fragmented. Their nuclei were large and vesicular. MacCallum's patch on the wall of the auricle was large, but not very conspicuous grossly, yet the sections revealed large numbers of Aschoff cells spreading apart the fibromuscular bundles in this area. The acute rheumatic vegetations on the mitral and aortic valve leaflets were typical. There was evidence of at least one previous attack of rheumatism in the form of old scarring and vascularization of the mitral valve. It was only after some search that perivascular scars, thought to be old, healed Aschoff bodies, could be found in the myocardium. Changes in the coronary vessels were quite evident. Large numbers, but not all, of the vessels about the size of the Thebesian vessels had swollen endothelial cells and edematous walls. Vessels of the magnitude of arterioles showed many areas of intimal thickening, edema, and cellular infiltration

of the adventitia. Rarely, the lumen was completely occluded. Alterations in the larger coronaries were essentially those of arteriosclerosis, with marked intimal thickening by old fibrous tissue, in which fat-laden cells were imbedded. Aschoff bodies were found in the fat surrounding the larger coronaries, but only mononuclear cells infiltrated the adventitia. Merely by chance, slides were prepared from the aorta; they showed two distinct acute rheumatic nodules in the adventitia. The sinusoids of the liver were widened, without perivascular scarring, and there was edema of the lungs.

COMMENT

During the initial rheumatic infection, which doubtless occurred in childhood, the illness probably was minimal, and the injury to the myocardium and valvular endocardium so slight that it was never recognized. Not until the patient developed acute congestive heart failure, at the age of 61 years, did she ever present any obvious symptoms or signs of cardiac disease. Although heart failure as the result of active carditis in cases of chronic rheumatic heart disease is common in the earlier decades of life, it is indeed rare in the later decades, in which heart failure is caused by some added factor, such as hypertension or coronary thrombosis. The absence of marked cardiac hypertrophy, significant valvular inadequacy, hypertension, and coronary artery sclerosis leads us to believe that this patient's congestive heart failure was caused solely by the active myocardial inflammation, evidenced by great numbers of huge Aschoff bodies which had destroyed large areas of muscle, swelling of the intact muscle fibers, and acute rheumatic lesions in the small coronary blood vessels.

Cardiac hypertrophy is a usual sequel of chronic congestive heart failure. Stretching of the fibers is the stimulus to hypertrophy. Hypertrophy is said to result regardless of whether the congestive failure is caused by a mechanical factor (hypertension, valvular distortion) or infectious myocarditis. This case, with its evidence of a severe, acute myocardial inflammation, leads us to doubt whether acute myocarditis, per se, can cause cardiac hypertrophy. The slight hypertrophy which was found might well be ascribed to mechanical strain produced by preexistent distortion of the mitral valve.

CONCLUSION

A case of acute rheumatic fever in a woman 61 years of age, with extensive, acute, rheumatic myocarditis, is reported. Attacks of paroxysmal nocturnal dyspnea, associated with congestive heart failure, were the outstanding clinical features.

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Department of Reviews and Abstracts

Selected Abstracts

Harington, C. R., Pochin, E. E., and Squire, J. R.: A Simplification of the Evans Blue Method of Blood Volume Determination. Clin. Sc. 4: 311, 1940.

A method is described by which Evans blue can be extracted from plasma into butyl alcohol.

The dye can readily be estimated photoelectrically or colorimetrically in the final extract, which is free from plasma pigments and opacity.

The technique has been applied to the estimation of blood volume in fifteen normal individuals.

AUTHORS.

Wiggers, Carl J., and Wégria, René: Quantitative Measurement of the Fibrillations of the Mammalian Ventricles With Observations on the Effect of Procaine. Am. J. Physiol. **131:** 296, 1940.

The methods used for determining variations in the sensitivity or resistance of the ventricles to fibrillating agents are briefly reviewed and reasons presented why they are inadequate.

A new quantitative measure for the "fibrillation threshold" of the ventricles is proposed and tested. We believe it takes into account the irritability of nonrefractory myocardial fractions during the vulnerable phase of systole, and also any local state that may be necessary for the initiation of ventricular fibrillation. The procedure consists in measuring the current strength of brief D. C. shocks of constant duration (0.01 to 0.03 sec.) which are just able to induce fibrillation when applied during the vulnerable period of late systole to any fixed region of the ventricular surface.

The coefficients which modify the constancy of such thresholds were studied, and it was established that, despite repeated fibrillations and defibrillations, the threshold need not vary significantly and does not change abruptly over a period of four to five hours in untreated dogs. To obtain such relative constancy of fibrillation thresholds, the following conditions were observed: 1. Revival of the heart from fibrillation in less than thirty seconds. 2. Maintenance of the animal's blood temperature within 1 to 2° C. during the course of an experiment, which essentially determines surface temperature as well. 3. Stimulation at the same spot by D. C. shocks applied in alternate directions through nonpolarizable electrodes. 4. Allowance of an equilibration period of not less than fifteen minutes between one fibrillation and resumption of tests.

The applicability of the quantitative method was tested with reference to procaine which is reputed to increase the resistance of the ventricle to certain fibrillating agents. In six dogs, an increase in threshold, definitely beyond normal bounds was found; after treatment with procaine, a brief shock still fibrillates only when it is applied during the vulnerable period. We concluded that procaine raises the resistance of the ventricles to fibrillation but does not prevent its occurrence.

AUTHORS.

Wiggers, C. J., Wégria, R., and Piñera, B.: The Effects of Myocardial Ischemia on the Fibrillation Threshold—The Mechanism of Spontaneous Ventricular Fibrillation Following Coronary Occlusion. Am. J. Physiol. **131:** 309, 1940.

Alternate determinations of the fibrillation threshold of ventricles with a normal blood supply and during brief coronary occlusion were repeatedly made on the same animal. Rectilinear shocks 0.01 to 0.02 second in duration were applied to an identical area of the left ventricle. The milliampere value of a shock which, when applied during the vulnerable phase, induced fibrillation, served as the quantitative measure of the fibrillation threshold.

Significant reduction in the current strength required to fibrillate was noted during coronary occlusion, e.g., a decrease from 13.9 to 3 Ma. in one experiment. The vulnerable period of the ischemic region does not bear a normal relation to the ventricular pressure curve because the contraction of fibers in the ischemic area does not contribute to the pressure elevation and because the form and duration of the pressure curve are altered. Consequently, stimuli coinciding with the descending limb fibrillate, but those which fall on the horizontal portion of the pressure curve are ineffective in this respect.

The observations of Tennant and Wiggers that the ischemic area no longer shortens but stretches during systole cannot be interpreted as a complete failure of the effort contraction, but rather that the strength of effort is insufficient to overcome the stretching force of rising intraventricular pressure. When this force is removed during fibrillation, contractile waves are able to manifest themselves again.

Since ischemia reduces the fibrillation threshold to artificial stimuli and also causes formation of ectopic centers, the theory is put forward that such ectopic stimuli now become of threshold value for the hyperirritable myocardium and any one is capable of inducing fibrillation when it falls during either the vulnerable period of a normal beat or that of a premature beat excited from another ectopic center.

AUTHORS.

Goldberg, Harold, and Eyster, J. A. E.: The Relation of Contraction of Different Regions of the Ventricle of the Turtle to the Rise of Intraventricular Pressure. Am. J. Physiol. **131:** 416, 1940.

The rise of pressure in the ventricle of the turtle during systole is characterized by an initial slow rise, amounting to a few millimeters of mercury and lasting about 0.12 second. This is followed by an abrupt increase of the pressure gradient. Local shortening of various regions on the anterior surface of the ventricle begins during the initial period of pressure rise or within an interval of several hundredths of a second after its termination. Shortening in all regions thus occurs before the pressure has risen sufficiently to force blood into the great vessels and reduce the volume of the ventricle. This shortening is made possible by change in shape of the ventricle early in its contraction to approximate that of a sphere. Myograms from the surface of the ventricle of the turtle hence afford an adequate criterion for the onset of the local shortening process and for a comparison of electrical and mechanical events.

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Dow, Philip: The Development of the Anacrotic and Tardus Pulse of Aortic Stenosis. Am. J. Physiol. **131:** 432, 1940.

The anacrotic halt and tardus characteristics of the radial pulse in cases of aortic stenosis are shown to be due to the following factors:

1. Stenosis so reduces the violence of the systolic discharge that standing waves are not set up and the peripheral pulse reproduces the central pulse form with almost complete faithfulness.

2. The stenosis offers so much resistance to flow during mid-systole that the central pulse itself assumes the anacrotic and tardus characteristics.

AUTHOR.

Hedley, O. F.: Rheumatic Heart Disease in Philadelphia Hospitals. Public Health Reports **55**: 1707, 1940.

Of the 5,921 admissions involving rheumatic heart disease, rheumatic fever, Sydenham's chorea, and subacute bacterial endocarditis to Philadelphia hospitals from Jan. 1, 1930, to Dec. 31, 1934, 1,020 or 17.2 per cent, are known to have terminated fatally during the period under study or during an admission begun prior to Jan. 1, 1935. Excluding subacute bacterial endocarditis, apparently not superimposed on rheumatic heart disease, death occurred in 916, or 15.8 per cent of 5,801 admissions for rheumatic conditions. Of 4,653 cases, in contradistinction to admissions, of rheumatic conditions and subacute bacterial endocarditis, 1,020 or 21.9 per cent died. Excluding subacute bacterial endocarditis apparently not superimposed on rheumatic heart disease, 916 or 20.2 per cent of 4,538 cases resulted fatally.

Of the 916 fatal cases of rheumatic heart disease, 94.0 per cent were admitted primarily for rheumatic conditions or subacute bacterial endocarditis superimposed on rheumatic heart disease.

The cause of death of only 1.6 per cent of 916 fatal clinical cases of rheumatic heart disease appeared to be attributable directly to causes other than rheumatic heart disease or subacute bacterial endocarditis as a complication. Had this study been made on the basis of post-mortem examinations rather than clinical cases of rheumatic heart disease, this percentage in all likelihood would have been substantially increased.

With one possible exception the cause of 916 deaths involving rheumatic conditions, including subacute bacterial endocarditis as a complicating factor, was rheumatic heart disease. In no instance was death attributable to the arthritic manifestations of rheumatic fever or the cerebral manifestations of Sydenham's chorea.

Most deaths from rheumatic heart disease among patients who have been hospitalized occur in hospitals; almost three-fourths of the fatal cases are admitted only once.

The mean age at death from rheumatic heart disease, regardless of its association with subacute bacterial endocarditis, in both clinical and necropsy series is slightly less than 30 years. A slightly greater proportion of deaths is indicated among females than among males. Taking into consideration the less favorable economic circumstances of negroes, the proportion of deaths from rheumatic heart disease in hospitals among members of this race was not as great as might be expected. This is probably influenced by the age distribution of the negro population as a result of migration in recent years. The mean ages and age distributions do not suggest as great differences on the basis of race and sex as encountered in certain other types of heart disease.

Among 916 deaths from rheumatic heart disease, including subacute bacterial endocarditis as a complication, the greatest number occurred during the 20 to 29 year age period, with nearly as many in the 10 to 19 and 30 to 39 year age periods. Over 63 per cent occurred during these three age decades.

Over 50 per cent of deaths from rheumatic heart disease occurred among persons less than 30 years of age, while only 3 per cent occurred among persons over 60 years of age. Unlike many forms of heart disease, practically all deaths from rheumatic heart disease occur before the expiration of a normal span of life.

The age distribution of 732 deaths from rheumatic heart disease, exclusive of subacute bacterial endocarditis as a complication, manifested a double humped curve with peaks in the 10 to 19 and 30 to 39 year age decades.

Over 75 per cent of the deaths from rheumatic heart disease among persons under 30 years of age were apparently due to active rheumatic infection. Rheumatic infection is almost invariably the cause of death in children and young persons. With advancing age it becomes a less significant factor.

Peak of deaths from subacute bacterial endocarditis, regardless of its relationship to rheumatic heart disease, occurred during the 20 to 29 year age decade. The distribution by age decades and mean ages at death indicated death at ages younger by several years from subacute bacterial endocarditis superimposed on rheumatic heart disease than from other forms of subacute bacterial endocarditis.

These studies do not suggest that deaths from rheumatic heart disease in Philadelphia hospitals are more common among persons foreign born or of foreign extraction from among old-stock white Americans; if anything, the opposite obtains. This is probably influenced by the readiness with which various racial groups avail themselves of hospital facilities, their economic status, and the relative age of foreign groups, which is dependent in no small measure on the period of greatest immigration.

From the distribution of deaths by socioeconomic groups its is inferred that fatalities from rheumatic heart disease are disproportionately high among the laboring classes. Few deaths were indicated among professional men. In rheumatic heart disease choice of occupation is often limited because the disease develops during childhood; as a result persons with rheumatic heart disease are not as likely to engage in occupations requiring strenuous exertion as their social status would otherwise suggest.

Rheumatic heart disease results in approximately 200 deaths in Philadelphia hospitals annually; 165 are due primarily to rheumatic heart disease, while 35 are due to subacute bacterial endocarditis superimposed on rheumatic heart disease. In about 0.10 per cent of admissions from all causes, death is due to rheumatic heart disease.

Definite histories of rheumatic fever, Sydenham's chorea, or both of these conditions were obtained in 66.2 per cent of fatal cases. In nearly 80 per cent of instances in which the age at onset was given, the primary rheumatic manifestation developed prior to age 20 years; in less than 3 per cent was onset indicated among persons past 40 years of age.

The mean age at onset was 14.7 years, the mode, 9.3 years. The mean interval between the primary rheumatic manifestation and death was 13.4 years. Among 542 fatal cases in which the duration was ascertained, death resulted in less than one year in 13.5 per cent, in less than five years in nearly 32 per cent, and in less than ten years from the onset of the primary rheumatic manifestation in over 48 per cent.

At least 3.5 to 4.5 per cent of first attacks of rheumatic fever terminated fatally. If deaths from fulminating rheumatic carditis without arthritic manifestations of rheumatic fever are included, the percentage of initial case fatalities becomes even higher.

Despite the pre-eminence of Philadelphia as a medical center, mortality from rheumatic heart disease among hospital patients constitutes a distinctly local problem; at least 87.2 per cent of fatal cases were residents.

Nearly 8 per cent of deaths from rheumatic heart disease required investigation by the coroner's office because of their suddenness or because the patient had been unattended by a physician. To this extent rheumatic heart disease is a problem of interest to students of forensic medicine. Only 4.0 per cent of deaths from subacute bacterial endocarditis were the subject of a coroner's investigation.

The mean annual death rate from rheumatic heart disease in hospitals among Jewish persons was approximately the same as among white gentiles.

Twenty-one deaths among hospital patients with rheumatic disease occurred during pregnancy and the puerperium; sixteen were directly attributable to rheumatic heart disease. Of 116 pregnant women with rheumatic heart disease 18.1 per cent died. This high percentage is probably due to the severity of their condition on admission and to the likelihood that some cases of rheumatic heart disease which survived pregnancy were not identified for study because of obsolete filing systems and diagnostic nomenclature in some maternity hospitals.

AUTHOR.

Clahr, Jacob, Klein, Milton D., and Greenstein, Nathan M.: Rheumatic Heart Disease in Pregnant Women. New York State J. Med. **40**: 1242, 1940.

The establishment of the prenatal cardiac clinic has led to a threefold increase in the number of diagnosed cases of rheumatic heart disease in pregnancy.

The routine treatment of cases of rheumatic heart disease in pregnancy has been described.

The combination of adequate bed rest and digitalis has been the most effective means in the prevention of intra-partum and post-partum cardiac failure in rheumatic heart disease.

The only maternal deaths occurred in patients who had neither adequate bed rest nor digitalis.

AUTHORS.

Thacker, E. A.: Blood Pressure Studies on University Students, Including the Effect of Exercise on Essential Hypertension, Hypotension, and Normal Subjects. Ann. Int. Med. **14**: 415, 1940.

Students were divided into high, normal, and low blood pressure groups, a careful history taken on each, and the blood pressure reactions to a standard exercise test were recorded.

The increase in the systolic blood pressure following exercise was greatest in the high blood pressure group.

The systolic pressure after exercise in the hypertensive and hypotensive classes returned to normal more slowly than did the normal group.

The diastolic pressure during exercise fell on the average about as far below the basal level as the diastolic rose above the basal level with the cold test. This pressure returned to the original level somewhat more slowly in the hypertensive group.

There was a far greater difference between the usual or regular systolic blood pressure and the basal blood pressure in the hypertensive class than between those levels in the normal and low pressure groups. This criterion is a definite aid in discovering those cases in which the blood pressure should be checked more frequently.

The pulse rate following exercise returned to the basal rate within two minutes in the normal and low pressure subjects.

Vasomotor response from other factors plays a more important role in causing a systolic increase in blood pressure during exercise than does the pulse rate.

The same factors which govern the emotional status of an individual play an important part in the blood pressure reaction.

There is a definite hereditary factor in the regulation of blood pressure. The tendency toward essential high or low blood pressure is carried by the germ plasm from one generation to the next.

The amount of work or exercise apparently is not an etiologic factor in the production of essential hypertensive blood pressure.

The quantity of food intake may be an etiologic factor in producing high blood pressure, since there were two and one-half times as many heavy consumers of food in this class as in either of the other groups.

At least two or three subsequent rechecks should be made before a person is classified into the hypertensive or hypotensive group. This will prevent worry and anxiety in certain patients, and will be of considerable value to the physician in arriving at a correct diagnosis.

AUTHOR.

Sperling, Louis: Aneurysm of the Splenic Artery. Surgery **8**: 633, 1940.

A calcified aneurysm of the splenic artery is reported. The classical roentgenologic picture described by Lindboe was present and led to a correct preoperative diagnosis. The aneurysm was excised, together with the spleen, and the patient made an uneventful recovery. This is the twelfth recorded instance in which the patient recovered from operation for aneurysm of the splenic artery. Seven additional cases recorded in the autopsy material (33,810 autopsies) of the Department of Pathology of the University of Minnesota are added to those previously reported in the literature.

AUTHOR.

Gross, Louis: The Cardiac Lesions in Libman-Sacks Disease. With a Consideration of Its Relationship to Acute Diffuse Lupus Erythematosus. Am. J. Path. **16**: 375, 1940.

A study has been made of the hearts from twenty-three fatal cases of disseminated lupus erythematosus. The lesions observed were compared with the cardiac lesions in four cases of "atypical verrucous endocarditis" without lupus erythematosus. The characteristic macroscopic valvular and mural endocardial lesions of "atypical verrucous endocarditis" were observed in at least eight cases of lupus erythematosus. Moreover, microscopic lesions were observed in all of the twenty-three cases, particularly in the valve rings, valve leaflets, valve pockets, mural endocardium and pericardium. With few exceptions, these lesions were characteristic of the disease and many were identical with those observed in the four cases without lupus erythematosus.

In a discussion of terminology, it was pointed out that the pathologic lesions were not confined to the heart and might involve other organs, particularly the vessels of the kidney. On the other hand, these vascular lesions in other organs are sometimes mild and occasionally absent. Furthermore, it is possible that the clinical syndrome may occur without demonstrable cardiac lesions, although macroscopic or microscopic lacerations were invariably present in this series. The common denominator appears to be the clinical features described by Libman and Sacks, the cutaneous manifestations of diffuse lupus erythematosus being frequently but not invariably present. It is, therefore, suggested that the two groups of cases which have been previously called acute disseminated lupus erythematosus and atypical verrucous endocarditis, respectively, should be placed into the single category of Libman-Sacks disease.

Criteria are described for the pathologic diagnosis of Libman-Sacks disease on the basis of cardiac lesions, and these are distinguished from the lesions of rheumatic fever and subacute bacterial endocarditis.

AUTHOR.

Lewis, Thomas: The Adjustment of Bloodflow to the Affected Limb in Arteriovenous Fistula. Clin. Sc. **4**: 277, 1940.

Cases of arteriovenous fistula of the limbs are described in which the circulation to the distal part of the limb becomes restored to, or actually beyond, normal.

This compensatory increase appears to develop gradually over a period of years. It may be due in part to decreased vasomotor tone, but may also be due to vascular growth.

The growth of the distal arterial supply in arteriovenous fistula is of great interest from the general standpoint of collateral circulations. The idea that this growth may be explained simply by altered pressures or altered bloodflow, such as follow in the affected vessels as an immediate consequence of the original arterial lesion, cannot be supported. It is suggested that the growth is controlled by a stimulant, a chemical stimulant, arising locally as a product of the tissue need and acting locally.

AUTHOR.

Hines, Edgar A., Jr., and Barker, Nelson W.: Arteriosclerosis Obliterans. A Clinical and Pathologic Study. Am. J. Med. Sc. 200: 717, 1940.

A clinical study has been made of 280 consecutive cases of arteriosclerosis obliterans which were observed at the clinic. The clinical data have been supplemented by detailed gross and histologic studies of the arteries obtained from thirty-two legs that were amputated because patients had arteriosclerosis obliterans. The disease was found to occur predominantly among men between the ages of 50 and 70 years. There was no significant difference in racial incidence. The possible role of certain metabolic and chemical disturbances as etiologic factors has been emphasized. The lesions found in the arteries which were examined for pathologic changes consisted essentially of three components: 1. atheromatous plaques in the subintimal tissue, 2. degenerative changes in the medial coat, and 3. thrombosis. No significant difference was noted in the lesions of arteriosclerosis obliterans among diabetic and nondiabetic patients. The diagnosis and treatment are discussed in detail.

AUTHORS.

Katz, L. N., Sanders, A., Megibow, R. S., and Carlen, S.: Heart Size and Experimental Atheromatosis in the Rabbit. Am. J. Med. Sc. 200: 731, 1940.

The relationship of cardiac hypertrophy to coronary sclerosis was made the subject of direct experimental study.

For this purpose twenty-two rabbits were fed on a high cholesterin diet with the addition of the vitamin B complex. Sixteen of these rabbits subsequently developed moderate to severe atherosclerosis including involvement of the coronary arteries. The resulting heart weights of these were compared with eighteen rabbits serving as untreated controls and with 6 rabbits, which, although on the special diet, failed to develop gross or microscopic evidence of coronary or aortic atherosclerosis. All the rabbits were in the same age group with comparable body weights and the comparisons are therefore valid.

It was found that of the sixteen rabbits developing atherosclerosis twelve showed heart weights of more than 5 Gm. with an average cardiac weight of 6.3 Gm.; whereas the eighteen untreated control rabbits showed an average heart weight of 3.8 Gm., with only two hearts weighing more than 5 Gm.; while in the remaining six rabbits on the special diet but which did not develop atherosclerosis, only one heart weighed more than 5 Gm., and the average heart weight was 3.9 Gm.

To rule out factors other than the atheromatosis, direct systemic arterial blood pressures and pulse wave contours were obtained, and histologic sections carefully studied.

Evidence is presented to exclude atherosclerosis of the aorta, systemic arterial hypertension, aortic valvular defects, inflammatory disease of the myocardium, and other actions of the diet as factors in the production of cardiac hypertrophy in our experiments.

It is therefore concluded that coronary atherosclerosis per se produces cardiac hypertrophy in the rabbit. Ischemia of the heart appears to be involved in some way in the mechanism.

AUTHORS.

Burstein, Charles L., Marangoni, Bruno A., DeGraff, Arthur C. and Rovenstine, E. A.: Laboratory Studies on the Prophylaxis and Treatment of Ventricular Fibrillation Induced by Epinephrine During Cyclopropane Anesthesia. Anesthesiology **1**: 167, 1940.

Ventricular fibrillation may be inaugurated in the dog by injecting small doses of epinephrine (0.01 mg. per kilo) during cyclopropane anesthesia.

Procaine, and the related chemical compounds studied: p-amino benzoic acid, the calcium double salt of benzyl succinic and p-amino benzoic acids, sodium p-amino benzoate, when administered before epinephrine, protected from this type of ventricular fibrillation.

Procaine administered intravenously, when ventricular tachycardia followed the injection of epinephrine, arrested the progression to ventricular fibrillation, and recovery to normal occurred after a shifting of the pacemaker to the auricles and finally to the sinus node.

The intracardiac injection of procaine was found to be efficient in the treatment of 66 per cent of animals having developed ventricular fibrillation following epinephrine injection during cyclopropane anesthesia.

AUTHORS.

Good, Rankine: Convulsive Cardiazol Therapy in Cardiovascular Disorders. Brit. M. J. **2**: 624, 1940.

The main purpose of this paper is to demonstrate that cardiovascular disorders of even a severe degree—provided they are well compensated, and whether existing alone or in the presence of advancing years and of diseases of other systems—are not contraindications to the employment of convulsive therapy. Further, electrocardiographic examination in these cases provides no criteria indicative of how well or how badly the patient will stand up to the convulsion.

AUTHOR.

Hoffmann, Martin H., Sandler, Nathaniel, and Hecht, Hans: Paroxysmal Auricular Fibrillation Complicating Metrazol Shock Therapy. Am. J. Psychiatry **97**: 372, 1940.

A case of paroxysmal auricular fibrillation is presented. The arrhythmia persisted for five hours following the initial injection of metrazol which resulted in a strong epileptiform seizure. The various possible mechanisms are discussed and particular emphasis is laid upon the possibility of its "central" reflex origin.

AUTHORS.

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The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

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